2001

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Epidemiologic and clinical characteristics of fatal and nonfatal cases of Rocky Mountain spotted fever (RMSF) were compared to identify risk factors for death caused by this disease. Confirmed and probable RMSF cases reported through US national surveillance for 1981–1998 were analyzed. Among 6388 RMSF patients, 213 died (annual case-fatality rate, 3.3%; range, 4.9% in 1982 to 1.1% in 1996). Use of tetracycline-class antibiotics for treatment of RMSF increased significantly in the 1990s, compared with use in the 1980s. Older patients, patients treated with chloramphenicol only, patients for whom tetracycline antibiotics were not the primary therapy, and patients for whom treatment was delayed ≥5 days after the onset of symptoms were at higher risk for death. Although the case-fatality rate was lower in the 1990s than in the 1980s, risk factors for fatal RMSF were similar. Despite the availability of effective antibiotics, RMSF-related deaths continue to occur because of delayed diagnosis and failure to use appropriate therapy.

Rocky Mountain spotted fever (RMSF), an acute febrile illness caused by infection with *Rickettsia rickettsii,* is the most frequently reported fatal tickborne disease in the United States [1]. Annual case-fatality rates (CFRs) for RMSF have ranged from 2% to 18% since chloramphenicol and tetracycline-class antibiotics became available, during the late 1940s [1–8]. Recent reports indicate that annual CFRs for RMSF declined during the 1980s and into the early 1990s [1, 9, 10]. The factor or factors contributing to these declines are unknown. However, in the 1990s, treatment recommendations, especially for therapy for young children, were modified to encourage the use of tetracycline-class drugs as primary therapy for RMSF [1, 11–13].

Several studies have analyzed the epidemiologic and clinical characteristics associated with RMSF to determine risk factors for fatal disease [1, 4, 5, 8, 14]. Studies evaluating fatal and nonfatal cases of RMSF that occurred from the mid-1970s through the early 1990s have identified older patient age, black race, delay or lack of treatment, and failure to treat with a tetracycline antibiotic, individually or in combination, as risk factors for death [1, 2, 4, 5, 14–17]. Other studies evaluated probable and confirmed cases of RMSF and also included many cases that were unconfirmed by laboratory testing [1, 5, 17]. In the present study, we evaluated and compared epidemiologic and clinical characteristics of fatal RMSF cases with those for nonfatal RMSF cases during 1981–1998 in the United States.

Methods

RMSF cases were identified from RMSF surveillance case report forms submitted to the Centers for Disease Control and Prevention (CDC) by state health departments and private physicians [1, 9]. Confirmed and probable cases with known outcomes (fatal or nonfatal) that were reported during 1981–1998 were selected for this study. A classification of "confirmed" RMSF required signs and symptoms compatible with disease (e.g., fever, headache, and rash) and at least 1 confirmatory laboratory finding. Criteria for laboratory confirmation based on serologic testing included a ≥4-fold change in titer of antibody to *R. rickettsii* antigen between acute- and convalescent-phase serum specimens, measured by indirect immunofluorescence assay, complement fixation, latex agglutination, microagglutination, or indirect hemagglutination assay [9]. In addition, criteria for laboratory confirmation of RMSF included production of an amplicon of DNA using polymerase chain reaction assays with specific primers for *R. rickettsii;* demonstration of rickettsial antigens by immunostaining of biopsy or autopsy tissues; or isolation of *R. rickettsii* from clinical specimens. A "probable" RMSF case was defined by clinically compatible symptoms and a single titer, measured by indirect immunofluorescence assay, of ≥64; a single complement fixation titer of ≥16; or another supportive serologic finding (≥4-fold rise in titer or a single titer of ≥320, reactive with *Proteus* OX-19 or OX-2 antigens [Weil-Felix test], or a single titer of ≥128, measured by latex agglutination, indirect hemagglutination assay, or microagglutination test). Case reports that did not meet these criteria were considered to be "unconfirmed."

Demographic characteristics and clinical information for patients with fatal RMSF and patients with nonfatal RMSF were analyzed

Received 6 June 2001; revised 31 July 2001; electronically published 13 November 2001.

Presented in part: American Society for Rickettsiology–*Bartonella* as an Emerging Pathogen Group 2001 Joint Conference, Big Sky, Montana, August 2001.

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The Journal of Infectious Diseases 2001;184:1437–44

0022-1899/2001/18411-0010

for the period 1981–1998 and for 2 separate 9-year intervals, 1981–1989 and 1990–1998. Characteristics for analyses included patient age, type of antibiotic treatment, geographic region of residence, clinical signs and symptoms at presentation, and number of days from onset of illness to treatment (onset-to-treatment interval). CFRs were calculated for these characteristics, and comparisons between patients with fatal RMSF and those with nonfatal RMSF were made using odds ratios (ORs) and 95% confidence intervals (CIs). Age groups included patients <40 years and ≥40 years old and, for additional analysis, groups of patients <5, 5–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years old. Treatment therapies were grouped by use of any tetracycline without chloramphenicol (tetracyclines only), chloramphenicol without a tetracycline (chloramphenicol only), both a tetracycline and chloramphenicol (both), and neither a tetracycline nor chloramphenicol (neither). Geographic regions of residence were the US Bureau of the Census regions (i.e., Northeast, Midwest, South, and West). The clinical triad for RMSF was defined as the presence of fever and rash and a history of tick attachment [3]. For patients treated with chloramphenicol or tetracycline, onset-to-treatment intervals were grouped as <5 days and ≥5 days for analysis as a risk factor. Onset-to-treatment intervals for patients with fatal RMSF and patients with nonfatal RMSF were also compared by the Wilcoxon rank sum test [18]. To further evaluate antibiotic use, the difference in the frequency of use of tetracyclines and of chloramphenicol was compared by means of the χ^2 test. Hospitalization of patients was examined as a measure of severity of illness.

Multivariate logistic regression was done for the periods 1981–1998, 1981–1989, and 1990–1998 to further examine risk factors that were significantly associated with increased case fatality by fitting a series of hierarchical models to identify the best-fitting parsimonious model [19]. Risk factors were also examined separately for hospitalized patients and for patients with confirmed cases during 1981–1998.

Results

RMSF-associated mortality, 1981–1998. A total of 9968 RMSF case report forms were submitted to the CDC for 1981–1998. Of 6573 cases that met the definition for confirmed or probable RMSF, whether the patient was surviving or deceased was specified on the case report form for 6388 (97.2%). Confirmed cases accounted for 5178 (81.1%) of those 6388 cases. Cases from 46 states and the District of Columbia were reported. Reports were made of 213 RMSF-associated deaths in 29 states; 189 (88.7%) of those patients had confirmed cases. The average annual CFR was 3.3% for 1981–1998 (table 1). The annual CFR ranged from 4.9% in 1982 to 1.1% in 1996 (figure 1).

Risk factors for death from RMSF. To identify risk factors for death from RMSF, we compared epidemiologic and clinical characteristics of fatal cases of RMSF with those of nonfatal cases (table 1). Although most deaths (170) occurred in the South (figure 2), CFRs were similar across all regions of residence. CFRs for male and for female patients were similar (3.3% and 3.5%, respectively).

Black patients had a higher CFR (5.1%) than did white patients (3.3%), although the difference was not statistically significant. Further examination of characteristics by race indicated that black patients were less likely than white patients to present with a reported tick attachment, any rash, rash on the palms, clinical triad, headache, or myalgia. When the analysis was controlled for these factors, an association between race and increased risk for death was no longer seen (OR, 1.1; 95% CI, 0.5–2.3).

The risk of death was significantly higher for patients ≥40 years old than for those <40 years old (5.8% and 2.0%, respectively; table 1). The CFRs for age groups that included patients <40 years old ranged from 1.8% to 2.7%, whereas those for age groups that included patients ≥40 years old ranged from 4.5% to 7.8% (figure 3). The highest rates were among patients ≥60 years old (7.7%). The median age for patients with fatal cases of RMSF was 45 years, compared with 28 years for patients with nonfatal cases ($P < .001$). The risk for death was also significantly greater for RMSF patients who did not receive tetracyclines-only treatment, for those treated with chloramphenicol only, and for those who did not receive treatment with either a tetracycline or chloramphenicol. Onset-to-treatment interval information was available for 4208 (75.1%) of 5600 patients for whom specific therapy was reported. Patients with an onset-to-treatment interval of ≥5 days had a significantly higher risk of death than did those with an interval of <5 days. Other risk factors for death included temperature of ≥38°C at presentation, absence of headache at presentation, and absence of reported tick attachment.

Trends in fatal RMSF over time. The CFR for all patients was lower during 1990–1998 than during 1981–1989 (2.8% and 3.7%, respectively [OR, 0.7; 95% CI, 0.6–1.0]; table 1). The CFRs for male patients for the 1990s and the 1980s were similar (3.1 and 3.4, respectively), whereas the CFRs for female patients declined (2.3% and 4.3%, respectively [OR, 0.5; 95% CI, 0.3–0.8]). CFRs for white patients and black patients were similar during the 1990s and 1980s; an elevated risk for death was seen among black patients, but this difference was not statistically significant. The CFR for patients ≥40 years old was significantly lower during the 1990s than during the 1980s (3.9% and 7.5%, respectively [OR, 0.5; 95% CI, 0.3–0.7]), whereas the CFRs for patients <40 years old did not differ significantly (2.1 and 2.0, respectively; figure 3). However, during the 1990s, the CFRs for patients 40–49 and 50–59 years old were similar to those for patients <40 years old (OR, 1.3; 95% CI, 0.7–2.5). Older patient age, treatment with chloramphenicol only, no tetracyclines-only treatment, and treatment delay of ≥5 days were consistently associated with increased risk for death during the 1980s and the 1990s. Other risk factors for death during the 1980s included no report of tick attachment, no headache at presentation of illness, and no treatment with either a tetracycline or chloramphenicol. During the 1990s,

Table 1. Characteristics of patients with Rocky Mountain spotted fever, United States, 1981–1998.

Characteristic[a]	1981–1989			1990–1998			1981–1998		
	No. of deaths (CFR)	No. of survivors	OR (95% CI)	No. of deaths (CFR)	No. of survivors	OR (95% CI)	No. of deaths (CFR)	No. of survivors	OR (95% CI)
Total	142 (3.7)	3684		71 (2.8)	2491		213 (3.3)	6175	
Sex									
Female	61 (4.3)	1371	1.0	24 (2.3)	1005	1.0	85 (3.5)	2376	1.0
Male	80 (3.4)	2271	0.8 (0.6–1.1)	47 (3.1)	1446	1.4 (0.8–2.2)	127 (3.3)	3717	1.0 (0.7–1.3)
Age, years									
<40	53 (2.0)	2566	1.0	31 (2.1)	1454	1.0	84 (2.0)	4020	1.0
≥40	87 (7.5)	1067	3.9 (2.8–5.6)	40 (3.9)	984	1.9 (1.2–3.1)	127 (5.8)	2051	3.0 (2.2–3.9)
Race									
White	121 (3.7)	3161	1.0	59 (2.8)	2071	1.0	180 (3.3)	5232	1.0
Black	13 (5.1)	242	1.4 (0.8–2.5)	9 (5.1)	166	1.9 (0.9–3.9)	22 (5.1)	408	1.6 (1.0–2.5)
Region of residence									
Northeast	9 (4.4)	196	1.0	2 (1.2)	166	1.0	11 (2.9)	362	1.0
Midwest	13 (2.5)	498	0.6 (0.2–1.4)	14 (4.2)	321	3.6 (0.8–16.1)	27 (3.2)	819	1.1 (0.5–2.2)
South	117 (3.9)	2922	0.9 (0.4–1.8)	53 (2.6)	1954	2.3 (0.5–9.3)	170 (3.4)	4876	1.1 (0.6–2.1)
West	3 (4.3)	67	1.0 (0.3–3.8)	2 (4.3)	45	3.7 (0.5–26.9)	5 (4.3)	112	1.5 (0.5–4.3)
Tick attachment									
Yes	68 (2.9)	2242	0.6 (0.4–0.9)	32 (2.3)	1338	0.9 (0.5–1.6)	100 (2.7)	3580	0.7 (0.5–1.0)[b]
No	58 (4.7)	1187	1.0	22 (2.5)	856	1.0	80 (3.8)	2043	1.0
Symptoms									
Fever (temperature ≥38°C)									
Yes	135 (3.8)	3403	2.2 (0.7–7.0)	62 (3.1)	1937	6.0 (1.5–24.8)	197 (3.6)	5340	4.0 (1.6–9.8)
No	3 (1.8)	167	1.0	2 (0.5)	378	1.0	5 (0.9)	545	1.0
Headache									
Yes	91 (3.1)	2834	0.5 (0.3–0.8)	36 (2.0)	1759	0.7 (0.4–1.4)	127 (2.7)	4593	0.6 (0.4–0.9)
No	25 (5.8)	407	1.0	11 (2.7)	392	1.0	36 (4.3)	799	1.0
Myalgia									
Yes	89 (3.5)	2486	1.1 (0.7–2.0)	42 (2.4)	1691	1.6 (0.7–3.9)	131 (3.0)	4177	1.3 (0.8–2.0)
No	16 (3.0)	513	1.0	6 (1.5)	394	1.0	22 (2.4)	907	1.0
Rash									
Yes	112 (3.7)	2926	0.9 (0.6–1.5)	42 (2.7)	1513	1.5 (0.8–2.8)	154 (3.4)	4439	1.2 (0.9–1.8)
No	24 (4.0)	581	1.0	14 (1.8)	778	1.0	38 (2.7)	1359	1.0
Rash on palms									
Yes	54 (2.9)	1796	0.7 (0.5–1.1)	24 (3.2)	729	1.8 (1.0–3.3)[b]	78 (3.0)	2525	1.1 (0.8–1.5)
No	49 (3.9)	1206	1.0	22 (1.8)	1230	1.0	71 (2.8)	2436	1.0
Clinical triad[c]									
Yes	51 (2.9)	1714	0.7 (0.5–1.0)	21 (3.0)	683	1.5 (0.9–2.7)	72 (2.9)	2397	0.9 (0.7–1.2)
No	69 (4.3)	1534	1.0	26 (2.0)	1291	1.0	95 (3.3)	2825	1.0
Treatment									
Tetracyclines only									
Yes	30 (1.4)	2132	0.2 (0.1–0.3)	30 (1.6)	1867	0.3 (0.2–0.6)	60 (1.5)	3999	0.2 (0.2–0.3)
No	105 (7.0)	1405	1.0	25 (4.6)	519	1.0	130 (6.3)	1924	1.0
Chloramphenicol only									
Yes	67 (7.7)	804	3.3 (2.4–4.7)	12 (7.2)	155	4.0 (2.1–7.8)	79 (7.6)	959	3.7 (2.7–5.0)
No	68 (2.4)	2733	1.0	43 (1.9)	2231	1.0	111 (2.2)	4964	1.0
Both									
Yes	18 (4.4)	389	1.2 (0.7–2.1)	3 (3.1)	93	1.4 (0.4–4.7)	21 (4.2)	482	1.4 (0.9–2.2)
No	117 (3.6)	3148	1.0	52 (2.2)	2301	1.0	169 (3.0)	5449	1.0
Neither									
Yes	20 (8.6)	212	2.7 (1.7–4.5)	10 (3.5)	271	1.7 (0.9–3.5)	30 (5.8)	483	2.1 (1.4–3.2)
No	115 (3.3)	3325	1.0	45 (2.1)	2123	1.0	160 (2.9)	5448	1.0
Onset-to-treatment interval, days									
<5	29 (1.9)	1542	1.0	8 (1.0)	790	1.0	37 (1.6)	2332	1.0
≥5	73 (6.0)	1137	3.4 (2.2–5.3)	24 (3.8)	607	3.9 (1.7–8.8)	97 (5.3)	1742	3.5 (2.4–5.2)

NOTE. CFR, case-fatality rate; CI, confidence interval; OR, odds ratio.

[a] Variations in the no. of cases listed for each characteristic are due to unknown or missing responses.

[b] Confidence limit equals 1.0 because of rounding ($P < .05$).

[c] Fever, any rash, and tick attachment.

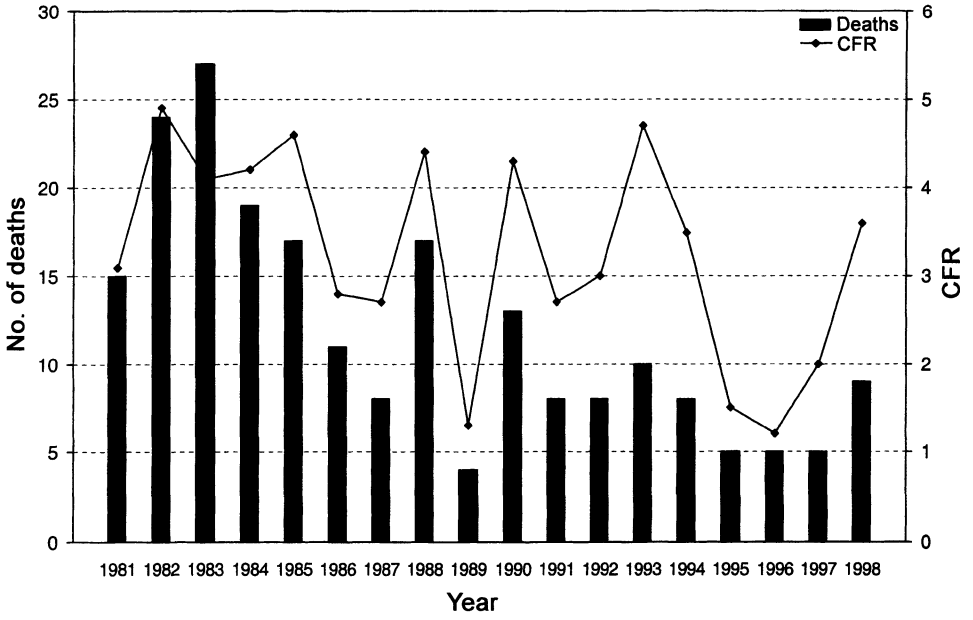

Figure 1. Annual no. of deaths and case-fatality rate (CFR) for Rocky Mountain spotted fever cases in the United States, 1981–1998

other risk factors included temperature ≥38°C and rash on palms at presentation.

Antibiotic treatment and outcome. Information on antibiotic treatment was provided for 5600 confirmed and probable RMSF cases (87.7%) with a known outcome during 1981–1998. Most RMSF patients (66.4%) were treated with tetracyclines only; 17.0% received chloramphenicol only, and 8.2% received both a tetracycline and chloramphenicol. The use of tetracyclines-only treatment increased in the 1990s (77.7%, vs. 58.9% in the 1980s; $P < .001$), whereas chloramphenicol-only treatment declined (6.8%, vs. 23.7% in the 1980s; $P < .001$). Treatment with both therapies also increased in the 1990s (11.1%, vs. 3.9% in the 1980s; $P < .001$).

To further evaluate the impact of chloramphenicol-only use among young patients, we stratified patients by age <10 years and ≥10 years for each 9-year period. Patients <10 years old were treated only with chloramphenicol significantly more often than were patients ≥10 years old during the 1980s (49.2% vs. 13.6%; $P < .001$). Chloramphenicol-only treatment during the 1990s remained significantly higher for those <10 years old than for those ≥10 years old (26.3% vs. 2.6%; $P < .001$). The CFR for patients <10 years old who were treated with chloramphenicol only did not change significantly in the 1990s, compared with the CFR for that group in the 1980s (4.3% [5 out of 115] and 2.6% [13 out of 509], respectively [OR, 1.7; 95% CI, 0.6–4.7]). No deaths were reported among 229 patients <10 years old who were treated with tetracyclines only during the 1990s, and 1 death was reported among 599 of such patients during the 1980s.

Overall, CFRs for patients in each drug treatment category did not differ between the 1980s and the 1990s (chloramphenicol only, 7.7% and 7.2%, respectively; tetracyclines only, 1.4% and 1.6%, respectively). The CFR for patients treated only with chloramphenicol during 1981–1998 was greater than that for patients treated only with tetracyclines (7.6% vs. 1.5% [OR, 5.5; 95% CI, 3.9–7.7]), a difference apparent during both 9-year periods. The CFR for patients treated only with tetracyclines differed from that for patients who did not receive antibiotic treatment (OR, 0.2; 95% CI, 0.2–0.4), whereas the CFR for patients treated only with chloramphenicol did not differ from that for patients who did not receive antibiotic treatment (OR, 1.3; 95% CI, 0.9–2.1). These findings were consistent for both time periods. CFRs for patients ≥40 years old were higher than those for patients <40 years old, both among patients treated with chloramphenicol only and among those treated with tetracyclines only. Further examination of the cases of patients <10 years old showed that the CFR for patients treated only with chloramphenicol was higher than the CFR for those treated only with tetracyclines (2.9% and 0.2%, respectively [OR, 17.8; 95% CI, 2.8–741.3]); for patients ≥10 years, a similar difference in CFRs was seen (15.0% and 1.7%, respectively [OR, 10.1; 95% CI, 6.8–14.9]).

Among patients treated with tetracyclines only, those with fatal cases of RMSF had experienced a longer delay before antibiotic treatment than had those with nonfatal cases (median, 6 and 4 days, respectively; $P = .003$); the same was true of patients treated with chloramphenicol only (median, 6 and 5 days, respectively; $P < .001$). For all RMSF patients, the median onset-to-treatment interval for both chloramphenicol-only and tetracyclines-only treatment was 5 days. Among patients treated <5 days after diagnosis, the CFR for those treated only with chloramphenicol was higher than for those treated only with

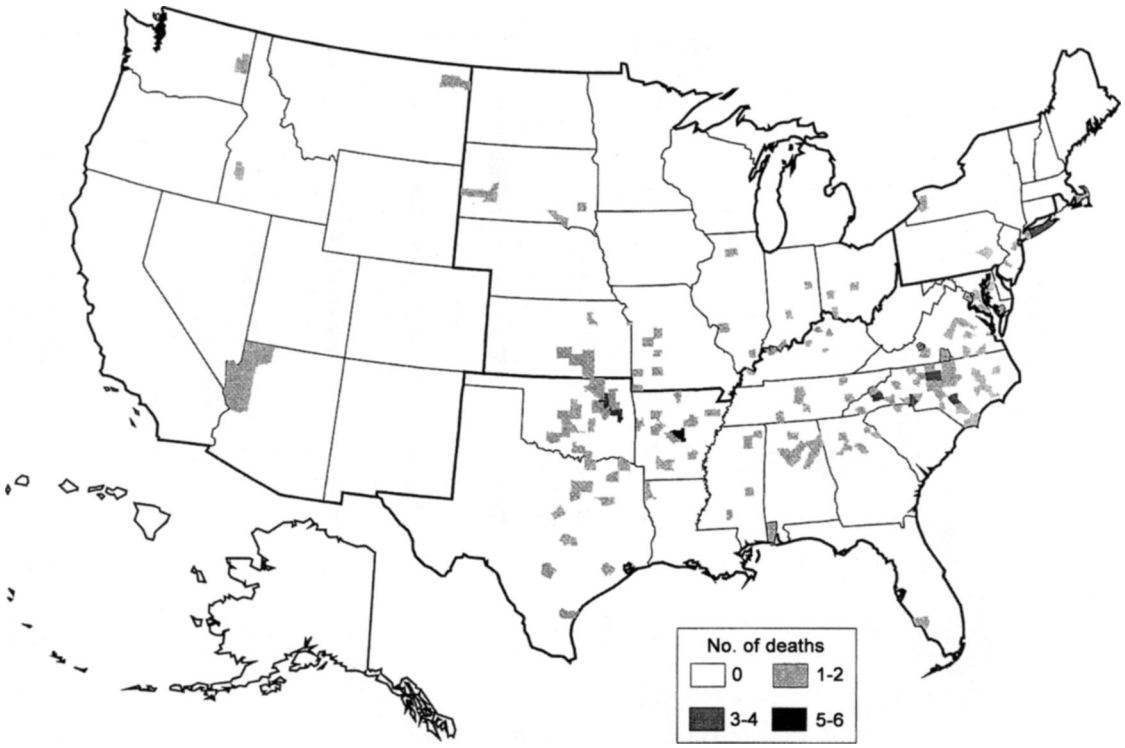

Figure 2. Geographic distribution of reported deaths due to Rocky Mountain spotted fever in the United States, 1981–1998. County of residence was available for 210 of 213 reported deaths.

tetracyclines (3.5% and 1.0%, respectively [OR, 3.7; 95% CI, 1.7–7.9]); this difference was also noted for patients treated ⩾5 days after diagnosis (12.2% and 2.5%, respectively [OR, 5.4; 95% CI, 3.3–8.7]).

Hospitalization, antibiotic treatment, and outcome. Hospitalization occurred among 4166 (65.5%) of the 6359 RMSF patients for whom this information was reported during 1981–1998. Patients with fatal RMSF were hospitalized more often than patients with nonfatal RMSF (95.7% and 64.5%, respectively [OR, 12.4; 95% CI, 6.3–24.2]). The CFR for hospitalized patients did not differ by time period (4.8% for 1981–1989 and 4.9% for 1990–1998, respectively). Hospitalized patients were more likely to be treated with tetracyclines only than with chloramphenicol only (57.8% and 23.3%, respectively; $P < .001$). The median number of days between onset of RMSF and treatment for hospitalized patients with fatal cases and for hospitalized patients with nonfatal cases was 6 and 4 days, respectively ($P < .001$).

Multivariate analyses. Multiple logistic regression indicated that older patient age, onset-to-treatment interval of ⩾5 days, no tetracyclines-only treatment, and chloramphenicol-only treatment remained significantly associated with death from RMSF during 1981–1998 (table 2). Risk factors remained the same when the analysis was restricted to patients with confirmed cases and to hospitalized patients (data not shown). For 1981–1989, the analysis showed that older patient age, onset-to-treatment interval of ⩾5 days, no tetracyclines-only treatment, and chloramphenicol-only treatment were significant risk factors. For 1990–1998, older patient age, onset-to-treatment interval of ⩾5 days, and chloramphenicol-only treatment were statistically associated with fatal RMSF.

Discussion

This study identified older patient age, delay in treatment, chloramphenicol-only treatment, and treatment that did not involve a tetracycline antibiotic as primary therapy as risk factors for death among RMSF patients in the United States during 1981–1998. These findings are largely consistent with risk factors identified individually or in combination with other epidemiologic and clinical characteristics in studies that examined RMSF deaths during the 1970s and the 1980s [1, 4, 5, 8, 14]. In this study, factors associated with death appeared to be consistent over time, with the following exceptions: the age for increased risk of death appeared to shift from patients ⩾40 years old during the 1980s to those ⩾60 years old during the 1990s, and the reported use of chloramphenicol for RMSF declined markedly and the use of tetracyclines increased during the 1990s, compared with use of these antibiotics during the 1980s. Treatment delay, which was identified as a risk factor in several other studies [3, 8, 14, 20], was clearly associated with increased risk for death among RMSF patients.

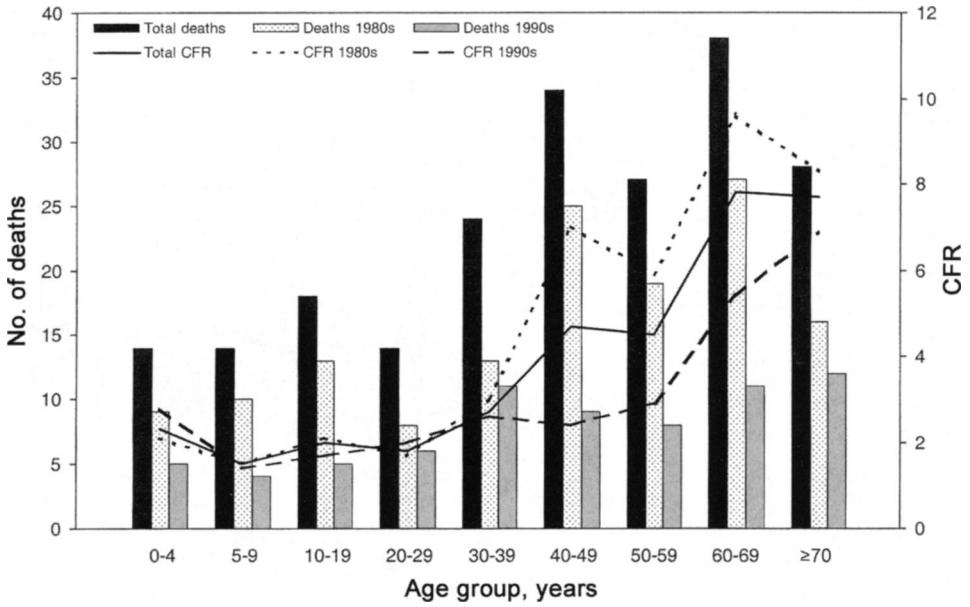

Figure 3. No. of deaths and case-fatality rates (CFRs) for Rocky Mountain spotted fever cases, by age group and time period, in the United States, 1981–1998.

Before the discovery of RMSF-specific antibiotic therapy, ~1 of every 5 patients infected with *R. rickettsii* died [21]. The original description of chloramphenicol in 1947 [22] was accompanied by a report showing that this antibiotic inhibits the growth of *R. rickettsii* in embryonated eggs and in experimentally infected animals [23]. Clinical experience with use of chloramphenicol to treat human patients with RMSF accumulated rapidly and showed that patients treated with this antibiotic had relatively rapid favorable clinical responses [24, 25]. The use of this antibiotic and of tetracycline-class drugs, which were also discovered in the late 1940s, resulted in dramatic declines in annual CFRs over the course of the next 50 years. Until relatively recently, it was thought that chloramphenicol and tetracyclines were equally efficacious for treatment of RMSF; however, recent epidemiologic studies that used CDC case report data have suggested that RMSF patients treated with chloramphenicol have a greater risk of dying than do persons who receive tetracycline as primary therapy [1, 17]. Findings from the present investigation corroborate these observations and are notable in the context of the separate univariate and multivariate analyses done in this study. During 1981–1998, CFRs for patients treated with chloramphenicol alone were significantly higher than CFRs for patients treated with a tetracycline. This observation was consistent among all patients in general, as well as among specialized cohorts, including the youngest patients (i.e., <10 years old), the most severely ill patients (i.e., hospitalized), and even among patients receiving specific therapy <5 days after onset of disease, the interval during which appropriate therapy has the greatest effect in reducing the probability of death [1, 3, 8].

Several in vitro studies comparing the bacteriostatic activities of chloramphenicol and tetracycline-class drugs against rickettsiae have shown that *R. rickettsii* is more susceptible to tetracyclines than to chloramphenicol [26, 27]. Clinical studies of experimentally induced RMSF in dogs showed no significant differences between chloramphenicol and tetracycline in alleviating clinical indicators of rickettsial infection [28]; however, no data exist from controlled, prospective clinical trials evaluat-

Table 2. Multivariate analysis of risk factors associated with death among patients with Rocky Mountain spotted fever, United States, 1981–1998.

Time period, risk factor	Maximum likelihood estimate[a]	SE	OR (95% CI)
1981–1998 (n = 4134)			
Age	1.6232	0.1966	5.1 (3.4–7.5)
Treatment			
Tetracyclines only	−1.0339	0.2836	0.4 (0.2–0.6)
Chloramphenicol only	0.9527	0.2792	2.6 (1.5–4.5)
Onset-to-treatment interval	1.0072	0.2031	2.7 (1.8–4.1)
1981–1989 (n = 2735)			
Age	1.7971	0.2274	6.0 (3.9–9.4)
Treatment			
Tetracyclines only	−1.1087	0.3249	0.3 (0.2–0.6)
Chloramphenicol only	0.9040	0.2993	2.5 (1.4–4.4)
Onset-to-treatment interval	0.9120	0.2338	2.5 (1.6–3.9)
1990–1998 (n = 1399)			
Age	1.0641	0.3929	2.9 (1.3–6.3)
Treatment with chloramphenicol only	1.7172	0.4291	5.6 (2.4–12.9)
Onset-to-treatment interval	1.2606	0.4156	3.5 (1.6–8.0)

NOTE. CI, confidence interval; OR, odds ratio.
[a] Calculated by multivariate logistic regression.

ing the relative efficacies of these drugs in humans. Chloramphenicol is still appropriate therapy for RMSF in some specialized situations [29]. Nonetheless, despite the limitations of incomplete and retrospectively collected data that are inherent to passive reporting, the findings from this study are consistent with and augment data from other epidemiologic analyses describing the superiority of tetracyclines over chloramphenicol as primary therapy for RMSF.

Changes in treatment recommendations for pediatric patients and the removal of the oral formulation of chloramphenicol from the US market in 1995 likely contributed to the decrease in the use of chloramphenicol during the 1990s [1, 11, 12]. In this study, the decline in CFR from the 1980s to the 1990s, particularly among patients $\geq$10 years old, may be associated in part with the decreased use of chloramphenicol and the increased use of tetracyclines for RMSF treatment in the 1990s. During the 1990s, children $<$10 years old still received chloramphenicol as the primary therapy for RMSF more often than all other age groups, reflecting a continued need for physicians to be informed that doxycycline is the recommended treatment for RMSF in children [11, 12, 30].

An increased CFR among black individuals has been reported in other studies [4, 15]; this has been ascribed to underreporting of nonfatal cases and increased misdiagnosis of RMSF among black individuals [4] or increased incidence of a glucose-6-phosphate dehydrogenase deficiency in this population [15]. However, as with earlier studies [1, 3], the present study did not find a significant difference between CFRs for black individuals and white individuals.

The data from the national RMSF surveillance system have limitations. Although RMSF is a nationally notifiable disease [31], fatal and nonfatal cases of RMSF can be missed and may pose a diagnostic dilemma for physicians in locations where the disease occurs infrequently [10, 11]. Moreover, state health departments may have differing criteria for defining and reporting RMSF cases, and some state health departments have revised their criteria for reporting RMSF cases to the CDC. Although criteria for reporting may change depending on the state, the specific data requested on and collected from case report forms have not changed since these forms were last modified, in 1981 [5]. In this context, risk factors identified in this study and earlier studies are limited to those data collected on the case report form [1, 17], which accounts in part for the consistent appearance of particular risk factors (e.g., specific antibiotic use, onset-to-treatment interval, and age). However, other risk factors (e.g., glucose-6-phosphate dehydrogenase deficiency) may not be identified in the surveillance case report form, because the form does not include specific queries about other medical conditions that may predispose patients to more-severe or fatal disease. The severity of the illness, which affects decisions about treatment and hospitalization, cannot be accurately ascertained with case report forms. Finally, the case report forms are not always fully completed and are completed with varying attention to detail.

RMSF continues to be a potentially lethal threat throughout much of the United States, and recognized risk factors for total RMSF death are largely unchanged since the 1980s. Despite enhanced awareness of tickborne diseases during the 1980s and 1990s [16, 32–34], diagnosis or treatment of RMSF may be delayed, and recommended treatment is not always administered; both of these situations may be associated with fatal consequences. Prompt treatment with tetracycline-class antibiotics within the first few days of onset of illness significantly reduces the risk of death [1, 11]. CFRs for RMSF in different geographic regions across the United States are similar, which suggests that, even in the region with the highest incidence of RMSF and, presumably, the greatest awareness of the disease (i.e., the South), treatment delays may occur and recommended therapy is not always provided. This observation suggests that, if deaths due to RMSF are to be further reduced in the United States, increased awareness and public health education regarding RMSF remain fundamental in achieving this goal.

Acknowledgments

We thank John O'Connor, for editorial assistance; Eric Mandel and Alison Mondul, for assistance in compiling and editing data; and the many physicians and state and local health departments that reported RMSF cases.

References

1. 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.
2. Hattwick MA, O'Brien RJ, Hanson BF. Rocky Mountain spotted fever: epidemiology of an increasing problem. Ann Intern Med **1976**;84:732–9.
3. Helmick CG, Bernard KW, D'Angelo LJ. Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. J Infect Dis **1984**;150:480–8.
4. Helmick CG, Winkler WG. Epidemiology of Rocky Mountain spotted fever 1975–1979. In: Burgdorfer W, Anacker RL, eds. Rickettsiae and rickettsial diseases. New York: Academic Press, **1981**:547–57.
5. Fishbein DB, Kaplan JE, Bernard KW, Winkler WG. Surveillance of Rocky Mountain spotted fever in the United States, 1981–1983. J Infect Dis **1984**;150:609–11.
6. Sexton DJ, Burgdorfer W. Clinical and epidemiologic features of Rocky Mountain spotted fever in Mississippi, 1933–1973. South Med J **1975**; 68:1529–35.
7. Smathers BR, Jones JL, Sy FS, Meyer P. Epidemiology of Rocky Mountain spotted fever in South Carolina, 1985–1990. J S C Med Assoc **1992**; 88:378–85.
8. Kirkland KB, Wilkinson WE, Sexton DJ. Therapeutic delay and mortality in cases of Rocky Mountain spotted fever. Clin Infect Dis **1995**;20:1118–21.
9. 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 **2001**;63:21–6.
10. 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.

11. Centers for Disease Control and Prevention. Consequences of delayed diagnosis of Rocky Mountain spotted fever in children—West Virginia, Michigan, Tennessee, and Oklahoma, May–July 2000. MMWR Morb Mortal Wkly Rep **2000**;49:885–8.
12. American Academy of Pediatrics. Rocky Mountain spotted fever. In: Pickering LK, ed. 2000 Red book: report of the Committee on Infectious Diseases. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics, **2000**:491–3.
13. Abramson JS, Givner LB. Should tetracycline be contraindicated for therapy of presumed Rocky Mountain spotted fever in children less than 9 years of age? Pediatrics **1990**;86:123–4.
14. Hattwick MAW, Retailliau H, O'Brien RJ, Slutzker M, Fontaine RE, Hanson B. Fatal Rocky Mountain spotted fever. JAMA **1978**;240:1499–503.
15. Walker DH. The role of host factors in the severity of spotted fever and typhus rickettsioses. Ann N Y Acad Sci **1990**;590:10–9.
16. Walker DH. Tick-transmitted infectious diseases in the United States. Annu Rev Public Health **1998**;19:237–69.
17. Fishbein DB, Frontini MG, Giles R, Vernon LL. Fatal cases of Rocky Mountain spotted fever in the United States, 1981–1988. Ann N Y Acad Sci **1990**;590:246–7.
18. Lehmann EL. Nonparametrics: statistical methods based on ranks. San Francisco: Holden-Day, **1975**.
19. Kleinbaum DG, Kupper LL, Muller KE, Nizam A. Applied regression analysis and other multivariable methods. 3d ed. Pacific Grove, CA: Duxbury Press, **1998**.
20. 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 **1978**;17:673–9.
21. Harrell GT. Treatment of Rocky Mountain spotted fever with antibiotics. Ann N Y Acad Sci **1952**;55:1027–42.
22. Ehrlich J, Bartz QR, Smith RM, Joslyn DA, Burkholder PR. Chloromycetin, a new antibiotic from a soil actinomycete. Science **1947**;106:417.
23. Smadel JE, Jackson EB. Chloromycetin, an antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections. Science **1947**; 106:418–9.
24. Pincoffs MC, Guy EG, Lister LM, Woodward TE, Smadel JE. The treatment of Rocky Mountain spotted fever with chloromycetin. Ann Intern Med **1948**;29:656–63.
25. Parker RT, Bauer RE, Lister LM, Woodward TE, Hall HE. Further experience in the treatment of Rocky Mountain spotted fever with chloramphenicol. Am J Med **1950**;9:308–14.
26. Ormsbee RA, Parker H, Pickens EG. The comparative effectiveness of aureomycin, terramycin, chloramphenicol, erythromycin, and thiocymetin in suppressing experimental rickettsial infections in chick embryos. J Infect Dis **1955**;96:162–7.
27. Raoult D, Roussellier P, Vestris G, Tamalet J. In vitro antibiotic susceptibility of *Rickettsia rickettsii* and *Rickettsia conorii:* plaque assay and microplaque colorimetric assay. J Infect Dis **1987**;155:1059–62.
28. Breitschwerdt EB, Davidson MG, Aucoin DP, et al. Efficacy of chloramphenicol, enrofloxacin, and tetracycline for treatment of experimental Rocky Mountain spotted fever in dogs. Antimicrob Agents Chemother **1991**;35:2375–81.
29. Walker DH, Sexton DJ. *Rickettsia rickettsii.* In: Yu VL, Merigan TC, Barriere SL, eds. Antimicrobial therapy and vaccines. Baltimore: Williams & Wilkins, **1999**:562–8.
30. Purvis JJ, Edwards MS. Doxycycline use for rickettsial disease in pediatric patients. Pediatr Infect Dis J **2000**;19:871–4.
31. Centers for Disease Control and Prevention. National electronic telecommunications system for surveillance—United States, 1990–1991. MMWR Morb Mortal Wkly Rep **1991**;40:502–3.
32. Fishbein DB, Dennis DT. Tick-borne diseases—a growing risk. N Engl J Med **1995**;333:452–3.
33. 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.
34. Parola P, Raoult D. Ticks and tickborne bacterial diseases in humans: an emerging infectious threat. Clin Infect Dis **2001**;32:897–928.