Therapeutic Delay and Mortality in Cases of Rocky Mountain Spotted Fever

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We conducted a retrospective cohort study of patients with Rocky Mountain spotted fever (RMSF) at a university hospital in order to assess the relationship between delay in treatment and mortality and to identify predictors of delay in initiating therapy. Patients with RMSF who received antirickettsial therapy within 5 days of the onset of symptoms were significantly less likely to die than were those who received treatment after the 5th day of illness (6.5% vs. 22.9%, respectively; $P < .03$). Ninety percent of patients were seen by a physician during this 5-day period, yet less than one-half of them received treatment before day 6. Three factors were independent predictors of failure by the physician to initiate therapy the first time a patient was seen: absence of a rash, presentation between 1 August and 30 April, and presentation within the first 3 days of illness. Until reliable early diagnostic tests become available, physicians may be able to decrease the mortality associated with RMSF by instituting empirical treatment of suspected cases within the first 5 days of illness.

Rocky Mountain spotted fever (RMSF), the most virulent rickettsial disease of the spotted fever group, is endemic in the southeastern United States and has been reported from every region in the continental United States. Before the introduction of antirickettsial agents approximately 50 years ago, reported case fatality rates associated with RMSF ranged from 13% to 25% and were said to be as high as 80% in some areas [1]. With the advent of effective therapy, the case fatality rates reported for RMSF dropped dramatically [2, 3]. However, despite the availability in recent years of more than one effective therapy, case fatality rates have continued to average 3%–5% [4]. Higher fatality rates persist for certain groups such as males and adults >30 years of age [5–8]. Moreover, permanent morbidity, although uncommon, can be devastating to the individuals who survive the acute phase of infection [9]. This persistent mortality and morbidity has been attributed almost entirely to delay in the recognition and treatment of this disease [10–14]. The association between therapeutic delay and adverse outcome derives largely from analysis of data collected for surveillance purposes [5–8, 15, 16]; however, this association has become a widely held dogma in the medical community.

We reviewed the courses of 94 patients with RMSF who were hospitalized at Duke University Medical Center (Durham, NC) over a 26-year period in order to reexamine and quantitate the effect of a delay in effective therapy on mortality in cases of RMSF. In addition, we identified clinical and epidemiological factors that predict diagnostic or therapeutic delay in this disease.

Methods

Patients. One hundred forty-eight consecutive patients with a discharge diagnosis of RMSF who had been hospitalized at Duke University Medical Center between 1966 and 1992 were identified through a search of coded discharge records, autopsy records, and serological reports. All charts were reviewed by one of us (D. J. S.). Demographic, clinical, and laboratory data were collected, and exact intervals between the onset of symptoms and the first visit to a physician and between the first visit and initiation of effective therapy were determined. Of the 148 patients, 105 met the criteria of the Centers for Disease Control and Prevention with regard to definite or probable RMSF [17]. Eleven of these 105 patients were excluded from the analysis because of missing information concerning the exact dates of onset of illness, first physician visit, or initiation of therapy (seven patients) or because of missing information concerning the presence or absence of a rash at the first physician visit (four patients). The remaining study population of 94 patients consisted of 52 definite and 42 probable cases.

Definitions. For the purposes of our analyses, the "RMSF season" was defined as the period 1 May to 31 July; cases occurring outside this period were considered to be "off-season." The onset of symptoms was defined as the first day of any of the following symptoms: fever, chills, rash, headache, or gastrointestinal symptoms (nausea, vomiting,

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abdominal pain, or diarrhea). The classic triad of symptoms consisted of fever, rash, and a history of contact with ticks.

A first visit to a physician was considered to be early if it occurred within the first 3 days of illness; otherwise, the first visit was considered to be late. Effective therapy was defined as treatment with a tetracycline derivative, chloramphenicol, or any combination thereof.

Complications were defined as hypotension (systolic blood pressure, <90 mm Hg for >2 hours), coma, severe thrombocytopenia (platelet count, $<50{,}000/mm^3$), or renal insufficiency (serum creatinine level, ≥3 mg/dL). Serum creatinine levels were never measured for 32 patients; of these, 16 were classified as having normal renal function on the basis of blood urea nitrogen levels that never exceeded 15 mg/dL. Data on renal function were insufficient for classification of the remaining 16 patients; these patients were thus not considered in the analysis of complications.

Statistical analysis. The OR was used as the measure of association between risk factors and outcome variables. The OR for the effect of late therapy on mortality (adjusted for the effect of age, race, and sex) was obtained from a logistic regression model. Logistic regression with variable selection by backward elimination was used to identify independent predictors of therapeutic delay among the following potential risk factors: age, race, sex, presence or absence of a rash at the first physician visit, seasonality, and the timing of the first physician visit.

Results

Patient characteristics. The ages of our patients ranged from 2 to 78 years; 37 patients (39%) were >30 years old. Of the 94 patients, 57 (61%) were males and 46 (49%) were nonwhite. Sixty-eight patients (72%) presented between 1 May and 31 July; thus, 28% of cases occurred during the off-season. Information regarding tick contact was available for 79 patients; only 40 (51%) of them reported definite contact with a tick. Fever and headache were almost universal findings, even at the first physician visit. Rash was observed in only 37 patients (39%) when they first sought medical attention; the classic triad of symptoms was present in 17 of the patients (18%) at that time. Gastrointestinal symptoms were present at the time of the first physician visit in 71 (83%) of 86 patients for whom this information was available.

The interval from the onset of symptoms to the first physician visit ranged from 0 to 17 days; 69 (73%) of 94 patients saw a physician within the first 3 days of illness, and 85 (90%) had seen a physician by day 5.

Only 26 patients (28%) received effective antirickettsial therapy on the day of the first visit to a physician. Treatment was initiated after day 5 of illness for 48 patients (51%). All 94 patients had received appropriate therapy by the 17th day of illness. Nineteen patients (20%) received both a tetracycline derivative and chloramphenicol; the remainder were treated with one or the other of these drugs.

The median length of hospitalization was 8 days (range, 1–99 days) for the 80 patients who survived. Fifty-two patients (55%) experienced at least one complication. Fourteen patients died; the case fatality rate (CFR) was 14.9%.

Relationship of late therapy to mortality. Patients who did not receive antirickettsial therapy before the 6th day of illness were significantly more likely to die of RMSF (CFR, 22.9%) than those who were treated on or before day 5 of symptoms (CFR, 6.5%; OR, 4.3; 95% CI, 1.1, 16.4). When adjusted for the effect of age, race, and sex, lack of effective therapy before day 6 remained a significant risk factor for mortality (OR, 5.3; 95% CI, 1.2, 23.3).

Nine patients first consulted a physician after day 5 of illness and therefore could not have started receiving effective therapy by day 5. When analysis was limited to the 85 patients who did visit a physician on or before the 5th day of illness, late therapy remained a strong predictor of mortality (CFR, 23.1% vs. 6.5%; adjusted OR, 5.4; 95% CI, 1.2, 24.1).

Predictors of therapeutic delay. Three factors were independent predictors of failure by the physician to initiate antirickettsial therapy at the patient's first visit (table 1). These included the absence of a rash, an early first visit to the physician, and an off-season presentation. The age, race, and sex of a patient were not significantly associated with a delay in the initiation of effective therapy.

Discussion

Late initiation of effective therapy is clearly associated with increased mortality in cases of RMSF. In our study, the odds of dying were more than five times greater for patients who did not receive antirickettsial therapy by day 5 of their illness than for those who were treated earlier. This finding with regard to a group of patients hospitalized for RMSF is consistent with the findings of other investigators who used less complete but more extensive surveillance data to generate and test similar hypotheses [7, 16].

Moreover, our study demonstrates that despite a clear increase in mortality among patients whose therapy is delayed beyond the 5th day of illness, a minority (49%) of patients actually receive effective antirickettsial therapy by day 5. In most cases, this delay in administering effective therapy is not due to the patient's failure to seek medical care. In fact, in our study 39 (81%) of the 48 patients who received treatment after day 5 of illness had visited a physician during the first 5 days but had not started receiving treatment.

Of the 64 patients who were seen by a physician before the fifth day of illness and were not treated for RMSF at that time, 25 (40%) did receive therapy by day 5, which suggests that some physicians were effectively observing patients with suspected RMSF and were intervening in a timely manner. The remaining 60% of patients, however, did not receive ther-

Table 1. Factors associated with failure to initiate therapy for Rocky Mountain spotted fever at the first physician visit.

Factor	Percent of patients not treated at first visit	Univariate OR	*P* value	Multivariable OR (95% CI)	*P* value
Rash at first visit					
Absent	89.5	10.0	.001	8.7 (2.7, 28.1)	.001
Present	46.0				
First Visit					
Early	81.2	1.7	.001	4.0 (1.1, 14.0)	.04
Late	48.0				
Season					
Low incidence	92.3	6.5	.007	11.8 (2.0, 69.5)	.007
High incidence	64.7				
Race					
Nonwhite	80.4	2.3	.09	...	...
White	64.6				
Sex					
Male	75.4	1.5	.4	...	...
Female	67.6				
Age					
>30 y	73.0	1.1	.9	...	...
≤30 y	71.9				

apy until after the fifth day of illness, suggesting either lack of close follow-up or a failure by the physician to consider RMSF as a diagnostic possibility.

The three significant predictors of therapeutic delay beyond the first physician visit underscore the difficulty in making a clinical diagnosis of RMSF, even in an area of endemicity. When a patient presents without the hallmark rash (or before the rash has appeared), the other findings associated with RMSF can be identical to those of a myriad of other (mostly viral) infectious diseases that commonly occur in the summer months. It is not surprising that absence of a rash was a predictor of failure by the physician to start antirickettsial therapy.

Given the relatively low incidence of RMSF, even during the summer, failure by physicians to treat it early during the off-season months is also predictable. However, since 18 (69%) of the 26 off-season cases occurred during the months of April and August, a higher index of suspicion on the part of physicians near the beginning and end of the RMSF season could result in the institution of earlier therapy in some cases of RMSF.

Seventy-five percent of our patients had visited a physician by the third day of illness, yet such an early first visit actually lessened the patient's chances of being treated for RMSF at that visit, even when the patient had a rash and presented during the summer months. Although it is often impossible to make a definitive clinical diagnosis in the earliest stages of a febrile illness, it is imperative that the patient with suspected RMSF receive clinical follow-up by the 5th day of illness. This approach would allow for earlier initiation of antirickettsial therapy for many patients.

In most cases, currently available diagnostic tests do not result in a definitive diagnosis of RMSF during the first week of illness. The use of direct fluorescent antibody for analysis of skin biopsy specimens is specific but lacks sensitivity and requires the presence of a rash, which is often not present during the first 3 days of illness [18]. Early studies of the use of PCR in analyzing blood and urine specimens have also demonstrated a lack of sensitivity, although with further refinements, PCR may prove clinically useful [18, 19].

Until tests that are useful for early diagnosis are available, a physician is left in a difficult position. It seems clear that therapeutic delay beyond the 5th day of illness contributes to increased mortality among patients with RMSF. However, it appears that the only currently available means of preventing this outcome is to suspect RMSF in virtually every patient with febrile illness, to arrange clinical follow-up by the 5th day of illness, and, if RMSF is still suspected at that time, to treat the patient empirically. Given the low incidence of RMSF relative to viral illnesses, even in areas where the disease is endemic, this approach is likely to result in the unnecessary administration of tetracycline derivatives to many patients. Conversely, even the most astute clinician who follows these conservative guidelines may be unable to prevent the death of a patient with RMSF.

Those who believe that late initiation of therapy for RMSF is associated with increased mortality should not jump to the conclusion that all or even most deaths can be attributed to physician error; this conclusion is unwarranted and potentially harmful. The widely held belief that "mortality is essentially zero when [RMSF is] treated early enough" [20] is not justified on the basis of the results of currently available

studies. Most of our knowledge about RMSF is derived from retrospective analyses such as ours, which was limited to data on hospitalized patients, and from analyses of surveillance data; these methods are limited by recall and selection bias, and in some cases, by substantial amounts of missing or unvalidated information [5–8, 10, 15, 16, 21]. Only one prospective study in which data on the interval between the onset of symptoms and the initiation of therapy has been published; it was limited by the small number of adverse events, and the results were inconclusive [22]. No study has produced data that support therapeutic delay as the sole determinant of mortality in RMSF. Such a position not only fosters unnecessary and unreasonable malpractice litigation, but also diverts attention from alternate explanations for the continued morbidity and mortality associated with this disease.

More attention needs to be directed toward the role of rickettsial virulence and host immunity in determining outcome in cases of RMSF. For instance, for unknown reasons men appear to be more likely than women to die of RMSF [5–7]. In our study, male sex was a much more powerful predictor of mortality than was late initiation of therapy (OR, 10.6; $P < .01$; data not shown). Whether racial differences in the severity of RMSF are directly or indirectly related to levels of glucose-6-phosphate dehydrogenase needs further investigation [23–25]. Strain variation among some rickettsiae is recognized, but the significance of this variation in relation to outcome in human infection is not known [26–28]. Perhaps infection with a virulent strain is more likely to result in death, even in the setting of appropriately timed therapy.

Of the many possible contributors to increased mortality in RMSF, the timing of antirickettsial therapy is the only one over which physicians have some control. Until definitive early diagnostic tests become available, empirical therapy within the first 5 days of illness in cases of suspected RMSF may increase survival.

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