

Tick-Borne Relapsing Fever in the Northwestern United States and Southwestern Canada

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Records from 182 cases of tick-borne relapsing fever (TBRF) were reviewed. In confirmed cases, there was febrile illness, and spirochetes were identified on peripheral blood preparations. In probable cases, there were clinical features of TBRF and either the same exposure as a confirmed case or serological (indirect fluorescent antibody test and western blotting [WB]) evidence of infection with *Borrelia hermsii*. Sera also were tested for antibody to *Borrelia burgdorferi*. We identified 133 confirmed and 49 probable cases of TBRF. A Jarisch-Herxheimer reaction was reported in 33 (54.1%) of 61 cases for which this information was available. Most patients who had antibodies to *B. hermsii* were serologically positive for *B. burgdorferi*, and WB demonstrated false positivity of testing for *B. burgdorferi*. Thirty-five (21%) of 166 cases were unreported to public health authorities. In 52 cases, there were more than two relapses before the diagnosis. This study demonstrates that TBRF is underrecognized and underreported and may be falsely identified as Lyme disease.

Relapsing fever is characterized by recurring episodes of fever and nonspecific symptoms (e.g., headache, myalgia, arthralgia, and abdominal complaints). Usually episodes last for several days and are then interrupted by cessation of symptoms. Untreated patients have had up to 13 febrile episodes [1]. The illness is caused by infection with *Borrelia* species that extensively vary their surface antigens [2, 3]. The infection usually responds to treatment with antibiotics such as penicillin, tetracycline, or erythromycin. Treatment may elicit the Jarisch-Herxheimer reaction (JHR) characterized by acute exacerbation of symptoms.

Spirochetes causing relapsing fever are transmitted to humans by exposure to infected lice (*Pediculus humanus*) or the bite of an infected tick (*Ornithodoros* species). The mean incubation period is 7 days (range, 4 to >18 days) [1]. *Borrelia recurrentis* causes louse-borne relapsing fever (LBRF or epidemic relapsing fever). Spirochetes are introduced by crushing the louse (e.g., when scratching), which releases the insect's

infected hemolymph and contaminates abraded or normal skin and mucous membranes. LBRF is associated with poor hygiene and catastrophic events; an estimated 15 million cases of LBRF and >5 million deaths due to LBRF occurred in Africa, eastern Europe, and Russia in this century [2].

Tick-borne relapsing fever (TBRF or endemic relapsing fever) is found throughout most of the world. It is endemic in the western United States, southern British Columbia, the plateau regions of Mexico and Central and South America, the Mediterranean, Central Asia, and throughout most of Africa. The tick vectors, *Ornithodoros* species, are argasid (soft) ticks with nocturnal feeding habits and painless bites. The primary reservoirs of *Borrelia* are rodents [2]. Unlike the body louse that lives only several weeks, *Ornithodoros* ticks may live many years between blood meals and harbor spirochetes for prolonged periods [2].

In Texas, cases have been associated with entering caves where the tick, *Ornithodoros turicata*, harbors *Borrelia turicatae* [2, 3]. In most other western states and southern British Columbia, *Borrelia hermsii* is transmitted by *Ornithodoros hermsi* at higher elevations at which patients often report exposure in rustic cabins, where rodents' nests may harbor these ticks [2].

Each year, many travelers and rural residents are exposed to the tick vector within the western United States and British Columbia. Although many physicians believe TBRF is a rare disease, 58 cases of TBRF in Washington residents during 1980–1993 were documented by Washington State [4]. Fourteen of these cases may have been acquired in a neighboring state. Unlike Lyme disease (LD), TBRF is not a nationally reportable communicable disease. Although two excellent re-

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views have been reported in the past several decades [1, 2], a detailed review of recent cases and their complications, epidemiology, entomology, and geographic distribution in the Northwest has not been undertaken. To provide this information and examine problems with serological diagnosis, we report the results of a review of 182 cases of TBRF acquired in the northwestern United States and southwestern Canada.

Methods

Epidemiological Investigation

Records were obtained from disease report forms through state health departments (Washington, 1980–1995; Oregon, 1980–1988 [no report forms were available for Idaho]), from laboratory records (British Columbia, 1983–1995), and by a literature search via MEDLINE of published case reports or case series of TBRF. In Washington and Idaho, TBRF is a reportable disease. TBRF is not reportable in British Columbia or Montana and ceased being reportable in Oregon after 1988. When patients could be contacted, they were asked about other persons who had the same exposure (e.g., slept in the same cabin) and had a similar illness. An attempt was made to contact patients with possible cases found in this manner and, if applicable, their physicians. Demographic, clinical, and geographic data were obtained by reviewing charts and by interviewing patients, patient contacts (e.g., parents of children), or physicians.

A confirmed case was defined as both a febrile illness and detection of spirochetes by microscopic examination of a Wright-Giemsa–stained peripheral blood smear or darkfield microscopy of a peripheral blood smear. A probable case was defined as a typical clinical history and either an exposure associated with a confirmed case or positive serology (indirect fluorescent antibody [IFA] test or ELISA confirmed by western blotting [WB]). JHR was defined as acute exacerbation of the patient's symptoms following treatment with an antibiotic. Medical records and disease report forms were reviewed for JHR-associated symptoms (hypotension, tachycardia, chills, rigors, diaphoresis, or marked elevation of temperature).

Statistical Analysis

Data were analyzed by using Epi-Info Version 5.01B software [5]. Frequencies and relative risks with 95% confidence intervals were calculated. Prevalence maps were generated by using Epi Map software [6].

Laboratory and Field Investigation

Fixed smears, prepared from EDTA-treated blood specimens and stained by a rapid Wright-Giemsa method, were screened by lightfield ($\times 1,000$) and darkfield ($\times 250$ and $\times 400$) microscopy. Motile spirochetes were detected in wet mounts of

EDTA-treated blood specimens by darkfield ($\times 250$) microscopy.

B. hermsii HS1 (ATCC [American Type Culture Collection] 35209) serotype 33 (=C) originated from *O. hermsi* collected near Spokane, Washington [7]. *B. hermsii* DAH was isolated at Rocky Mountain Laboratories (RML), Hamilton, Montana, from blood from a human with relapsing fever in Washington. *Borrelia parkeri* and *B. turicatae* were isolated from *Ornithodoros parkeri* and *O. turicata*, respectively, and were part of the RML bacterial reference collection. *Borrelia burgdorferi* B31 was isolated from *Ixodes scapularis* collected on Shelter Island, New York [8].

Borrelial cultures were maintained in Barbour-Stoenner-Kelly (BSK) II medium [9] at 34°C and passaged twice a week. Patient blood specimens (treated with EDTA) were inoculated into BSK II medium, incubated at 35°C, and examined for motile spirochetes each day for 2 weeks. BSK II medium is a modification of substrate initially devised to cultivate *B. hermsii* [10]. Organisms were identified as *B. hermsii* with use of a species-specific monoclonal antibody [11].

Whole-cell lysates of spirochetes were subjected to one-dimensional SDS-PAGE with use of Laemmli buffer [12], and a vertical gel electrophoresis system (GIBCO BRL, Gaithersburg, MD) was used to separate proteins following the instructions of the manufacturer.

Whole-cell lysates underwent electrophoresis in one-dimensional acrylamide gels and were blotted onto nitrocellulose membranes by using the Towbin buffer system [13] and a Trans-Blot Cell (Bio-Rad, Richmond, CA) following the instructions of the manufacturer. The membranes were blocked overnight at room temperature with 50 mM Tris (pH, 7.4), 150 mM NaCl, 5 mM EDTA, and 0.05% Tween 20 (Sigma, St. Louis) and subsequently incubated with human serum samples diluted 1:100. Bound antibodies were detected directly by means of autoradiography with ^{125}I -labeled protein A.

Cultured spirochetes of *B. hermsii* HS1 (serotype 33) and *B. burgdorferi* B31 were removed from BSK II medium by centrifugation, rinsed twice in PBS, and mixed with fresh, washed sheep RBCs (these cells provide a negative background for comparison and an internal check for nonspecific binding of conjugate). Thin smears of each of these suspensions were made on glass slides, air-dried, fixed with methanol, wrapped with foil, and kept at -20°C until used. Human serum samples were tested with both species at eight twofold serial dilutions from 1:16 to 1:2,048, and bound antibodies were labeled with a 1:100 dilution of fluorescein isothiocyanate (Kirkegaard and Perry Laboratories, Gaithersburg, MD)–conjugated goat antibody to human IgG (heavy and light chains) and examined by fluorescence microscopy.

Selected serum samples were analyzed for antibodies reactive to *B. hermsii* and *B. burgdorferi* by ELISA methods at the Centers for Disease Control and Prevention (CDC), Fort Collins, Colorado, and at a commercial laboratory; IFA testing and immunoblotting for antibodies to *B. hermsii* and *B. burgdorferi*

Table 1. Demographics for 182 patients with TBRF.

Variable	No. (%) of patients
State or province of exposure* (<i>n</i> = 182)	
Washington	60 (33.0)
Oregon†	46 (25.3)
Idaho	40 (22.0)
British Columbia‡	26 (14.3)
Montana‡	1 (0.5)
Other	2 (1.1)
Unknown	7 (3.8)
Gender (<i>n</i> = 182)	
Male	104 (57.1)
Female	78 (42.9)
Age (<i>n</i> = 166)§	
Younger than 18 years of age	48 (28.9)
5 years of age or younger	10 (6.0)
Newborn (congenitally acquired disease)	1 (0.6)
Circumstance of exposure (<i>n</i> = 135)	
Visited or live in cabin or rural home	103 (76.3)
Recent outdoor activity (e.g., hiking)	23 (17.0)
Exposure uncertain or unknown	9 (6.7)
Rodent type present at exposure site (<i>n</i> = 46)	
Mice	19 (41.3)
Squirrels	16 (34.8)
Chipmunks	14 (30.4)
Rats	6 (13.0)

NOTE. *n* = no. of patients for whom this information was available; TBRF = tick-borne relapsing fever.

* Methods of case ascertainment varied by state.

† TBRF has not been a reportable disease in Oregon since 1989.

‡ TBRF is not a reportable disease.

§ Age range for 166 patients, newborn to 81 years.

|| There were more than one type of rodent at some exposure sites.

were performed at RML as previously described [14]. Whenever possible, acute- and convalescent-phase serum samples were obtained.

Results

Epidemiological and Clinical Data

We identified 133 confirmed and 49 probable cases of TBRF (table 1), of which 10 cases were previously reported [15–18]. The median age of the patients was 33 years (range, birth to 81 years). Of 35 female patients 15 to 44 years of age, four (11.4%) were pregnant during their illness, and one gave birth to an infected infant. Onset of illness was common during the spring and summer months (figure 1), although cases also occurred during the winter. The locations of exposure sites were usually rural cabins or homes, often located on or near a body of water. Several of the dwellings were permanently or frequently occupied, well-constructed residences.

Of 69 cases with rodent information, 50 (72.5%) noted that rodents were present at the exposure site. In 46 cases, the type of rodent seen was indicated (table 1). The median elevation at which exposure occurred in 89 cases was 2,131 feet (range,

100–6,436 feet). The geographic distribution of acquisition sites is presented in figure 2.

Many patients had several relapses before their infection was diagnosed. The median maximum recorded body temperature was 40°C (104°F) (range, 37.2°C–41.7°C [99°F–107°F]). Proteinuria and hematuria were relatively common, occurring in 18 (46%) of 39 persons and 11 (30%) of 37 persons, respectively. More than 90% of adult patients and ~80% of pediatric patients had a total WBC count of $\leq 14,000/\text{mm}^3$. Of 38 patients for whom a total WBC count, differential blood cell count, and platelet count were measured, 27 (71%) had a normal WBC count, >5% band forms, and thrombocytopenia. Clinical data are summarized in tables 2 and 3.

Laboratory and Field Investigation

Microscopy confirmed the presence of spirochetes in 133 patients. In 31 stained blood smears examined at Sacred Heart Medical Center in Spokane, Washington, organism concentrations ranged from one bacterium per five oil immersion fields (OIFs) to five or more spirochetes per OIF.

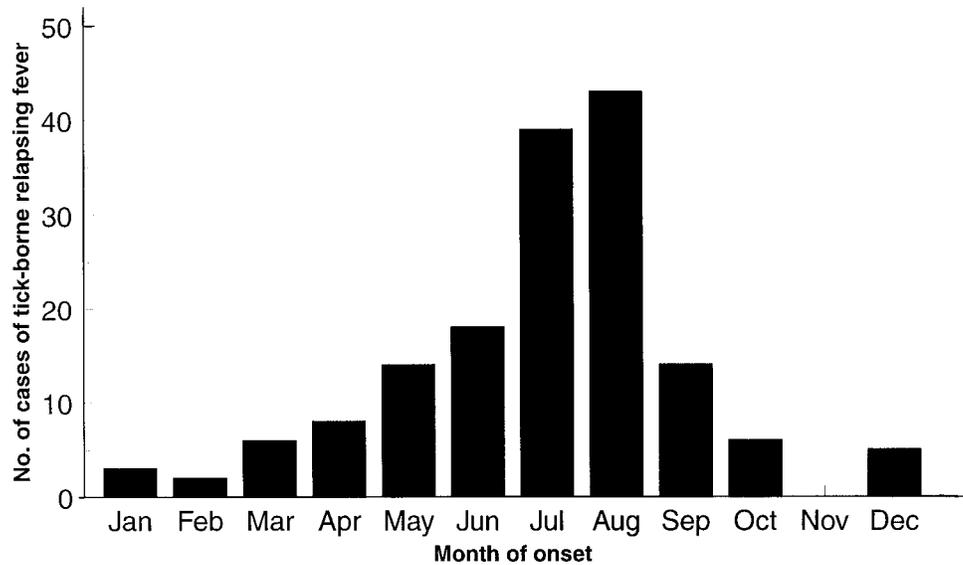
Three of the confirmed cases of TBRF that occurred in 1994–1995 were discovered when blood smears, which were initially determined to be negative at an outpatient clinic, were examined again at Sacred Heart Medical Center. Up to five spirochetes were identified per OIF. Organisms had been overlooked in two cases, and only an automated differential count was done in the third case.

Blood samples from 18 patients were cultured in BSK II medium. Spirochetes were identified in 12 of these samples (smears of initial peripheral blood or blood obtained at admission); 10 patients had not received prior antibiotic therapy, and their blood cultures were positive. Blood cultures were typically positive within 24 hours, and all yielded growth within 48 hours.

Two patients received prior antibiotic therapy and had negative cultures. In one case, blood collected immediately on arrival at the hospital (within 1 hour of taking antibiotic therapy) revealed nonmotile and sluggishly motile spirochetes. Rare, nonviable spirochetes were observed in the blood from the other patient, who was treated with ceftriaxone 4–5 hours earlier in a referring institution. In the remaining six culture-negative cases, the blood specimen was collected during an afebrile interval, and both peripheral blood smears and blood cultures were negative.

Serology (primarily IFA testing) was performed on >80 serum samples from patients. A representative sample of data from immunoblotting (WB) and IFA testing, performed at RML, is given in table 4; results of IFA testing for four of the patients were previously presented [14]. Antibody to GlpQ antigen was identified in cases 1–12, 16, and 17 (table 4). Limited ELISA testing by the CDC (10 cases; data not shown) paralleled results from RML. Results of IgM ELISA performed at a commercial laboratory were available for six patients. The

Figure 1. Cases of tick-borne relapsing fever by month of onset during 1980–1995 in British Columbia, Idaho, Oregon, and Washington. Data for 158 cases are presented; in 24 cases, the month of onset was unknown.



quantitative IgM indices (data not shown) did not differentiate *B. hermsii* from *B. burgdorferi* (table 4, cases 14–19). Thus, method-independent cross-reactivity was detected in most of the assays (table 4).

The number and intensity of reactive antigens determined by WB differentiated antibodies to *B. hermsii* from those to *B. burgdorferi* (figure 3). For most patients who had titers of IFA to *B. hermsii* of $\geq 1:2,048$, antibodies bound to protein bands when the sera were reacted with lysates of *B. burgdorferi*; both the number and intensity of bands were variable, but

typically 66-, 39- to 41-, and 20- to 22-kD proteins were evident (figure 3).

In case 1 (table 4), there was a history of a TBRF-like illness (relapsing fevers [maximum temperature, 105°F], severe headache, thrombocytopenia, and increased band form count) 9 years before culture and smear examination confirmed TBRF in 1993. His blood smear was not examined for spirochetes in the earlier illness, and he was not treated. After 6 to 8 weeks of relapses, he had spontaneous resolution. This patient (and three other patients with confirmed cases) was exposed to the

Figure 2. Geographic distribution of cases of tick-borne relapsing fever in British Columbia, Washington, Oregon, and Idaho by county of exposure. Numbers represent the number of cases per county during 1980–1995.

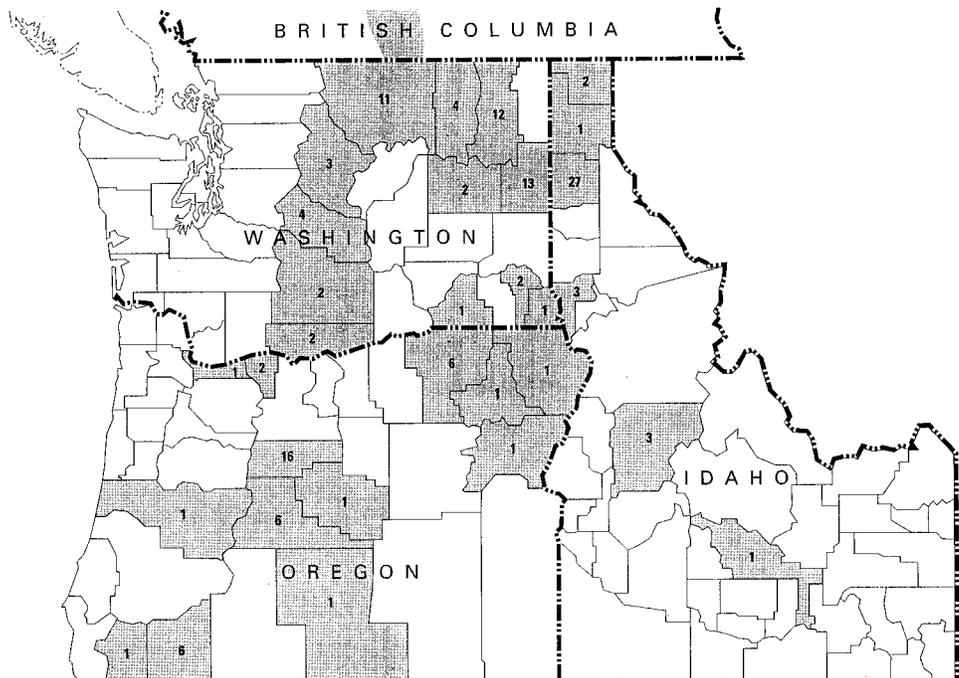


Table 2. Signs and symptoms of TBRF.

Variable	No. of patients with sign or symptom/no. of patients for whom information was reported (%)		
	Total (n = 182)	Confirmed TBRF (n = 133)	Probable TBRF (n = 49)
No. of relapses			
0	16/77 (20.8)	14/62 (22.6)	2/15 (13.3)
1	9/77 (11.7)	7/62 (11.3)	2/15 (13.3)
2	20/77 (26.0)	17/62 (27.4)	3/15 (20.0)
3	24/77 (31.2)	17/62 (27.4)	7/15 (46.7)
4	5/77 (6.5)	4/62 (6.5)	1/15 (6.7)
5	1/77 (1.3)	1/41 (2.4)	0/36
6	2/77 (2.6)	2/41 (4.9)	0/36
Headache	98/104 (94.2)	82/85 (96.5)	16/19 (84.2)
Myalgia	94/102 (92.2)	74/81 (91.4)	20/21 (95.2)
Chills	77/87 (88.5)	67/74 (90.5)	10/13 (76.9)
Vomiting	55/78 (70.5)	46/63 (73.0)	9/15 (60.0)
Nausea	53/70 (75.7)	45/58 (77.6)	8/12 (66.7)
Arthralgia	50/69 (72.5)	30/47 (63.8)	20/22 (90.9)
Abdominal pain	24/55 (43.6)	19/41 (46.3)	5/14 (35.7)
Diarrhea	14/57 (24.6)	9/46 (19.6)	5/11 (45.5)
Dry cough	13/49 (26.5)	11/39 (28.2)	2/10 (20.0)
Photophobia	12/48 (25.0)	11/38 (28.9)	1/10 (10.0)
Rash	11/61 (18.0)	10/49 (20.4)	1/12 (8.3)
Neck pain	10/42 (23.8)	8/32 (25.0)	2/10 (20.0)
Eye pain	10/38 (26.3)	6/28 (21.4)	4/10 (40.0)
Dysuria	6/48 (12.5)	6/37 (16.2)	0/11
Confusion	6/16 (37.5)	4/12 (33.3)	2/4 (50.0)
Jaundice	5/50 (10.0)	4/39 (10.3)	1/11 (9.1)
Hepatomegaly	5/52 (9.6)	3/40 (7.5)	2/12 (16.7)
Dizziness	4/16 (25.0)	3/12 (25.0)	1/4 (25.0)
Splenomegaly	3/53 (5.7)	2/43 (4.7)	1/10 (10.0)
Conjunctival injection	2/44 (4.5)	1/33 (3.0)	1/11 (9.1)
Meningitis	1/45 (2.2)	1/35 (2.9)	0/10
Eschar	1/47 (2.1)	1/37 (2.7)	0/10
Nuchal rigidity	1/44 (2.3)	1/34 (2.9)	0/10

NOTE. TBRF = tick-borne relapsing fever.

same rustic cabin before both of these illnesses. Following the single acute episode during 1993, IFA testing of his acute-phase serum revealed titers of antibodies to *B. hermsii* and *B. burgdorferi* of 1:2,048 and 1:128, respectively (table 4). WB revealed >20 intense reactive bands for *B. hermsii* and more than five bands of variable intensity for *B. burgdorferi* (data not shown).

In addition, WB with whole-cell lysates of *B. hermsii* and GlpQ antigen and IFA assays were useful in making the diagnosis for persons with previously undiagnosed cases who had had compatible disease syndromes in residences associated with an index case (23 cases associated with 11 residences in which IFA titers ranged from 1:128 to \geq 1:2,048 and antibody to GlpQ antigen was exhibited [data not shown]).

WB with whole-cell lysates or GlpQ antigen was not positive for two patients for whom tests for IgM were positive (cases 18 and 19, table 4). Acute-phase serum samples were obtained

from both patients, but convalescent-phase serum samples could not be obtained. In case 13, treatment was administered 2 days after disease onset, and IFA testing of acute- and convalescent-phase serum samples was negative.

Recognition of TBRF was often inadequate. During review of medical records, we found no cases of TBRF at the hospital in Coeur d'Alene, Idaho (located in a lake-resort town where 25 patients had reported exposure). At Sacred Heart Medical Center, seven (44%) of 16 patients were discharged with a diagnosis of LD. In addition, 35 cases (21%) were unreported to public health authorities.

JHR

Sixty-one cases contained information that could be evaluated to determine the presence or absence of JHR. Thirty-three patients (54.1%) had JHR (table 5). Twenty-nine (87.9%) of these patients had confirmed cases. Ten of 16 patients for whom temperature was recorded had a temperature of \geq 40°C (104°F). Chills, rigors, diaphoresis, tachycardia, and hypotension were common.

Information on the time to onset of JHR following antibiotic administration was available for 11 patients. JHR occurred within 2 hours and >3 hours of administration for 10 patients and one patient, respectively, including a tetracycline-induced JHR that occurred while the patient was riding in an automobile after leaving the pharmacy and resulted in admission to the intensive care unit.

Several possible risk factors for JHR were analyzed. These factors included age; sex; the presence of dysuria, thrombocytopenia, proteinuria, and microhematuria; >5% band forms in a differential WBC count; and choice of antibiotic. A statistically significant association was found only for the presence of microhematuria. Patients who had microhematuria were 0.4 times less likely to develop JHR than were persons who did not have microhematuria (six of 19 vs. 13 of 18, respectively; RR, 0.4; 95% CI, 0.2–0.9).

Discussion

TBRF has been recognized as endemic in the West since it was reported in Colorado in 1915 [19]. It has since been recognized throughout most of the Northwest, including Washington (1927), Idaho (1931), British Columbia (1932), and Oregon (1940) [1, 20, 21]. Cases have been reported sporadically throughout the Northwest, with a notable outbreak that occurred in a troop of Boy Scouts and their scoutmasters in Spokane County, Washington [7]. Before 1969, Washington had reported only four cases of TBRF [7]. After the outbreak of 11 cases in Spokane County in 1969, awareness apparently increased, and Fihn and Larson [22] reported 30 more cases that occurred in Washington and Oregon during 1965–1978.

Although TBRF is acquired in most of the western United States [7], its geographic distribution has not been described

Table 3. Results of clinical laboratory studies for cases of tick-borne relapsing fever.

Result	Median value, range (no.*)		
	Total	Confirmed cases	Probable cases
WBC count ($\times 1,000/\text{mm}^3$)	7.4, 3.1–19.5 (77)	7.4, 3.3–19.5 (65)	6.2, 3.1–18.1 (12)
% segmented neutrophils	67, 16–86 (59)	67, 16–85 (51)	69, 43–86 (8)
% band forms	14, 0–86 (52)	15, 0–86 (46)	2, 0–24 (6)
% monocytes	5, 1–21 (43)	5, 1–21 (38)	4, 1–7 (5)
Lowest recorded platelet count ($\times 1,000/\text{mm}^3$)	88, 7–385 (59)	84, 7–385 (50)	228, 46–344 (9)
Blood urea nitrogen level (mg/dL)	14, 4–46 (34)	14, 4–46 (29)	10, 9–21 (5)
Creatinine level (mg/dL)	0.9, 0.4–3.3 (39)	1.0, 0.4–3.3 (32)	0.9, 0.5–1.0 (7)
Erythrocyte sedimentation rate (mm/h)	61, 0–129 (30)	64, 0–129 (26)	34, 13–67 (4)

* Number of cases for which this result was available.

since the report of an outbreak at the North Rim of Grand Canyon National Park in 1973 [23]. The present investigation extends the recognized geographic distribution of TBRF and demonstrates the magnitude of disease in this region. TBRF and LD are currently reportable in Washington. This study suggests that TBRF may be more prevalent than LD in this state, where (during 1991 to 1994) only 11 serologically confirmed cases of LD were reported compared with 24 reported

cases of TBRF in the same period [4]. Improvement in diagnosis and reporting could clarify the true incidence of both diseases.

This study demonstrates several important aspects of TBRF, including a relatively high frequency of JHR, geographic clustering, and poor recognition and reporting. The clinical signs and symptoms we observed are generally similar to those noted in previous reports. The disease was often characterized by a

Table 4. Method-independent serological cross-reactivity of whole-cell lysate antigens of *Borrelia hermsii* and *Borrelia burgdorferi* in serum samples from patients with confirmed or probable tick-borne relapsing fever.

Case no.	Diagnostic category	Result of serological method					
		IFA testing*		Immunoblotting for		IgM ELISA	
		<i>B. hermsii</i>	<i>B. burgdorferi</i>	<i>B. hermsii</i>	<i>B. hermsii</i>	<i>B. burgdorferi</i>	
1	C, M	1:2,048	1:128	+ [†]	NT	NT	
2	C, M	1:2,048	1:64	+	NT	NT	
3	C, M	1:2,048	1:2,048	+ [†]	NT	NT	
4	P, M	1:2,048	1:2,048	+ [†]	NT	NT	
5	P, M	1:2,048	1:256	+	NT	NT	
6	P, M	1:1,024	1:2,048	+ [†]	NT	NT	
7	P, M	1:512	1:128	+	NT	NT	
8	C, M	1:512	1:64	+	NT	NT	
9	C, S	1:512	1:16	+	NT	NT	
10	C, M	1:256	1:64	+	NT	NT	
11	C, S	1:128	1:64	+	NT	NT	
12	C, S	1:128	1:32	+	NT	NT	
13	C, S	1:16 [‡]	1:16 [‡]	NT	NT	NT	
14	C, M	NT	NT	NT	+	+	
15	C, S	NT	NT	NT	+	+	
16	P, M	1:2,048	1:2,048	+ [†]	+	+	
17	C, M	1:2,048	1:32	+	+	+	
18	C, S	1:128	1:16	+	+	+	
19	P, M	1:32	1:16	+	+	+	

NOTE. C = confirmed case; M = one or more relapses; NT = serum not tested or not available; P = probable case; S = single acute episode; + = seroreactive assay (see text).

* Serum dilutions designated 1:2,048 are $\geq 1:2,048$.

[†] Also demonstrates multiple bands of protein in *B. burgdorferi* on immunoblots.

[‡] Titer is $< 1:16$.

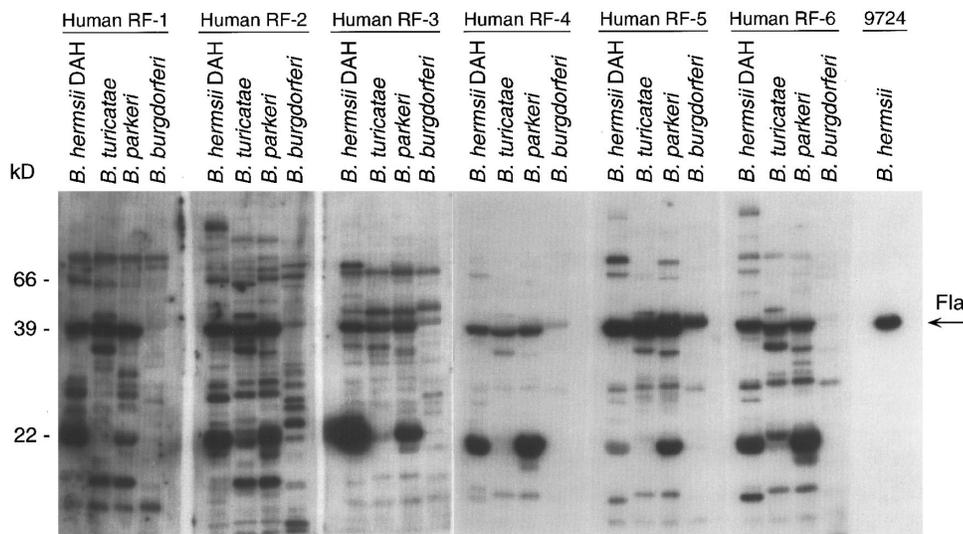


Figure 3. Immunoblot analysis of convalescent-phase serum samples from six patients with tick-borne relapsing fever (RF). Serum samples were diluted 1:100 and tested with whole-cell lysates of the four species of *Borrelia* spirochetes shown. In the far right panel, the monoclonal antibody 9724 to flagellin (Fla) indicates the position of the 39-kD Fla. Estimated molecular masses in kD are shown on the far left.

very high temperature, headache, myalgia, arthralgia, nausea, and vomiting. Fifty percent of the patients had a recorded temperature of $\geq 40^{\circ}\text{C}$ (104°F). Many patients relapsed more than two times, even though medical attention was sought during the febrile episodes; this finding demonstrates the lack of recognition many physicians have for this disease despite its regional endemicity.

Thrombocytopenia was common in this case series. We documented platelet counts of $\leq 20,000/\text{mm}^3$ in five cases, but no major bleeding complications were found. In contrast, LBRF is more frequently associated with bleeding complications (e.g., epistaxis, purpura, hemoptysis, hematemesis, bloody diarrhea, hematuria, subarachnoid and cerebral hemorrhages, splenic rupture, and retinal hemorrhage) [2].

Of the less frequently observed conditions, dysuria occurred in 12.5% of patients, proteinuria occurred in 46%, and microhematuria occurred in 30%. These symptoms suggest an as yet undescribed pathophysiology. The large numbers of circulating spirochetes seen in patients with this disease could possibly cause renal glomerular or tubulointerstitial disease, and spiro-

chetes have been described in urine from patients with acute TBRF [24]. Thrombocytopenia could explain microhematuria. Our study lacked the sample size needed to examine this possible link.

TBRF often occurred during the spring and summer months. However, unlike many other tick-borne diseases, TBRF also occurred during the winter. This winter occurrence of TBRF most often results from human activity that alters the behavior of the tick vector [25]. When humans enter and warm infested cabins during the winter, ticks are stimulated by warmth and carbon dioxide to seek out and feed on the occupants. *Ornithodoros* species may lay dormant for several years awaiting a blood meal, and some species do not require a blood meal from an infected host to harbor *Borrelia*.

The diagnostic standard for TBRF is detection of spirochetes in peripheral blood smears. Three main factors may contribute to poor detection: inexperience of the microscopist, increased use of automated differential counts, and examination of blood in the asymptomatic interval when spirochetes are absent from the circulation or are present in amounts below the level of detection. Increasingly, as a cost-saving maneuver, laboratories have discontinued manual differential counts unless specifically ordered. We recommend that a manual differential count be performed in the setting of an appropriate exposure history with the combination of flulike symptoms (especially high-grade fever and headache) and thrombocytopenia. Although culture (in the absence of previous therapy) is sensitive, delay in diagnosis, high cost, storage instability, and difficulty in establishing stable strains are important limitations for this method. Culture of spirochetes is primarily a research tool.

Currently, serological testing is limited to research, public health, and a few commercial laboratories. Serological testing is complicated by the ability of spirochetes causing relapsing fever to extensively alter their surface proteins [26]. Twenty-four serotypes were obtained from a single clone of *B. hermsii*

Table 5. Frequency of symptoms after initial therapy for 33 patients with tick-borne relapsing fever who had the Jarisch-Herxheimer reaction.

Symptom	No. of patients with symptom/ no. for whom information was reported (%)
Temperature of $\geq 40^{\circ}\text{C}$ (104°F)	10/16 (62.5)
Chills	20/23 (87.0)
Rigors	15/20 (75.0)
Diaphoresis	10/15 (66.7)
Tachycardia	10/20 (50.0)
Hypotension	18/23 (78.3)

[27]. The expression and regulation of the variable major proteins were reviewed recently [28]. In addition to variable major proteins, other structural proteins of *B. hermsii* cross-reacted with a variety of bacterial species, in particular with *B. burgdorferi* [29–32]. When rabbit antiserum to *B. hermsii* and serum from a patient with TBRF were reacted with *B. burgdorferi* antigens [30], WB revealed 11 and six bands, respectively [31].

We demonstrated method-independent cross-reactivity of *B. hermsii* and *B. burgdorferi* from data generated by three laboratories. In most cases, high titers of antibody to *B. hermsii* in patient serum samples reacted with *B. burgdorferi* antigens in IFA assays, ELISA, and WB. In addition, WB often demonstrated six or more bands of protein in *B. burgdorferi* in sera from patients with high titers of antibody to *B. hermsii*, and if sera were analyzed only with *B. burgdorferi* antigens, it was possible to satisfy the proposed CDC criteria for the diagnosis of LD (i.e., two of three IgM bands or five to 10 IgG bands) [33]. Therefore, in regions where both diseases occur, serological tests may generate misdiagnosis [14, 31]. Since serological testing of patients with chronic syndromes of LD is not uncommon, clinicians and laboratorians should be alert to the significant cross-reactivity of *B. burgdorferi*, *B. hermsii*, and other infectious organisms [29–32].

No systematic investigation of TBRF serology has been done with IFA testing, EIA, or WB. During this investigation, which is essentially descriptive, serum collections were frequently retrospective. For example, of the six patients for whom IgM assays were performed at a commercial laboratory, only one had a comparative IFA assay done in the acute phase of disease. All others were tested by IFA assays 6 weeks to 1 year following the acute episode. In addition, in this series, nearly 80% of patients had multiple relapses. Consequently, appreciably different titers were not found in acute- and convalescent-phase serum samples, when available.

In 1996, Schwan et al. [14] reported the potential utility of a recombinant antigen, GlpQ, for the specific diagnosis of relapsing fever. In that study and this investigation, patients with TBRF and titers of IFA of $\geq 1:256$ had antibody to GlpQ antigen, and probable or confirmed cases in which titers of IFA were 1:64 to 1:128 sometimes evoked antibody to GlpQ antigen. Therefore, we believe that titers of IFA of 1:64 to 1:128 represent an indeterminate range and that titers of $\geq 1:256$ represent a diagnostic range.

Case 1 was unusual in that TBRF appeared to have occurred twice (1984 and 1993). Typically, patients with TBRF have titers of IFA in acute-phase serum that range from undetectable to 1:512, and WB of these serum samples reveals zero to <10 protein bands. However, testing of this patient's serum (obtained during his first febrile event of the 1993 illness) revealed extreme results (IFA titer, $\geq 1:2,048$; WB, >20 bands). In fact, this patient's serum had more reactivity with *B. hermsii* antigens than any serum sample that had previously been tested at RML (T. G. Schwan, unpublished data). The immunologic data, history of a TBRF-like illness in 1984, and

the association of multiple cases of TBRF at the rustic cabin he had occupied immediately prior to both disease episodes suggest that this patient likely acquired infection with TBRF on two separate occasions.

The increased symptoms seen during JHR often include hypotension, chills or rigors, a marked rise in temperature, and a general increase in other symptoms. Our data revealed that 33 (54.1%) of 61 patients for whom this information was available had JHR. During JHR, one patient complained that he felt like he was "going to die," and this sensation has been reported previously [34]. LBRF nearly always results in JHR when treatment with tetracycline is administered; however, 59% of patients with TBRF caused by *Borrelia duttonii* (prevalent in East and Central Africa) have been described to have JHR, and no JHRs were reported in one series of TBRF caused by *Borrelia crocidurae* (prevalent in West and Northeast Africa and the Middle East to Iran) [2]. A review of cases of TBRF in Colorado revealed that seven of 21 treated patients had JHR [35]; on the basis of this study's data, JHR apparently occurs often enough to warrant keeping these patients under observation for ~ 2 hours after initiation of treatment. Experimentation with the dose of antibiotic used at the commencement of treatment of LBRF (e.g., treatment with a lower than recommended dose) has led some investigators to conclude that this modification decreases the frequency of JHR [36]. For patients who have TBRF, a prospective study of variable initial antibiotic dosages would be useful, as only anecdotal information is available.

In this study, JHR occurred 0.4 times less frequently in patients who had microhematuria. Bacterial infection of the lower urinary tract is a well-recognized cause of hematuria [37], and spirochetes have been described in urine [24]. Higher levels of bacteremia have been reported to be associated with an increased likelihood of patients with LBRF developing JHR [38], although this study had a small sample size. We suspect that high levels of bacteremia would lead to spirocheturia, microhematuria, and a possible increase in the frequency of JHR, although we did not observe this.

This study included data for four pregnant women, one of whom gave birth to an infected infant. One woman in her 12th week of pregnancy had an extremely high temperature (41.8°C [107.2°F]) during JHR but gave birth to a normal full-term infant. The other two women had uncomplicated deliveries and apparently normal infants. Congenital TBRF has been previously reported [39]. Infection in pregnant women may be more severe than in other persons, and miscarriages are common [1]. Transmission may be transplacental or may possibly be secondary to traversing the birth canal [40].

Our review of medical records supports the notion that TBRF is an underrecognized disease. JHR was unanticipated for many of these patients. Two patients underwent a bone marrow biopsy to evaluate their recurring febrile illness. Leukemia was suspected in one of these patients because of the low platelet count; the other patient was evaluated as having a fever of

unknown origin. In addition, two patients whose cases were associated with multiyear outbreaks at residences and who had serological evidence of TBRF were evaluated for leukemia in remote institutions. Another patient underwent temporal artery biopsy because the syndrome included fever and headaches. In spite of a characteristic history, commonly TBRF was considered only after laboratory personnel reported identification of spirochetes on blood smears.

In Canada, only British Columbia has reported locally acquired TBRF. In 1933, in the first report of an outbreak of TBRF in this province [21], six cases occurring in the Kootenay region were described. Hearle [41], on the basis of known vector-organism competency and tick behavior, hypothesized that *O. hermsi* was the probable vector. Spiller [42], in 1986, reported two cases from the Okanagan Valley in southern British Columbia. Since 1984, we are aware of additional cases that occurred and were acquired in British Columbia, but we were unable to obtain the clinical records for review [42, 43]. All recently described cases occurred in the Okanagan Valley [44, 45], and no cases were reported in the Kootenay region since 1933. We believe that cases have been acquired there because this region is geographically similar to and near a known focus of infection in the northwestern United States; however, inquiry about TBRF in the Kootenay region revealed no further cases.

Our study demonstrates that TBRF is an endemic disease in the northwestern United States and southwestern Canada. Despite the relatively large number of cases observed near the border between eastern Washington and northwestern Idaho, reporting of TBRF underestimates the magnitude of the problem. More than 25 cases of TBRF were acquired at Coeur d'Alene Lake, Idaho, during the study period. However, a review of medical records over 5 years at the local hospital in this region revealed no cases. The present data most likely significantly underestimate the actual number of cases of TBRF in this region.

Oregon data were available only from disease report forms from 1980 to 1988. No records of TBRF were available for review from the Idaho State Department of Health and Welfare. In 1987, TBRF was removed from Montana's reportable disease listing. On the basis of these observations in the northwestern United States and southwestern Canada, we believe that TBRF is an underreported disease.

To further evaluate TBRF, several of the authors are participating in an ongoing surveillance for cases acquired in all states of endemicity. Reports of cases and consultation can be initiated by telephoning one of the authors (Donald E. Anderson, Jr., phone 800-442-8535).

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