Tick-Borne Relapsing Fever

CLAY ROSCOE, M.D., and TED EPPERLY, M.D., *Family Medicine Residency of Idaho, Boise, Idaho*

Tick-borne relapsing fever is characterized by recurring fevers separated by afebrile periods and is accompanied by nonspecific constitutional symptoms. It occurs after a patient has been bitten by a tick infected with a Borrelia spirochete. The diagnosis of tick-borne relapsing fever requires an accurate characterization of the fever and a thorough medical, social, and travel history of the patient. Findings on physical examination are variable; abdominal pain, vomiting, and altered sensorium are the most common symptoms. Laboratory confirmation of tick-borne relapsing fever is made by detection of spirochetes in thin or thick blood smears obtained during a febrile episode. Treatment with a tetracycline or macrolide antibiotic is effective, and antibiotic resistance is rare. Patients treated for tick-borne relapsing fever should be monitored closely for Jarisch-Herxheimer reactions. Fatalities from tick-borne relapsing fever are rare in treated patients, as are subsequent Jarisch-Herxheimer reactions. Persons in endemic regions should avoid rodent- and tick-infested areas and use insect repellents and protective clothing to prevent tick bites. (Am Fam Physician 2005;72:2039-44, 2046. Copyright © 2005 American Academy of Family Physicians.)

▶ **Patient information**: A handout on tick-borne relapsing fever, written by the authors of this article, is provided on page 2046.

Tick-borne relapsing fever (TBRF) is transmitted by Ornithodoros ticks infected with one of several different Borrelia spirochete species, most commonly *Borrelia hermsii* and *Borrelia turicata*. The highest concentrations of TBRF in the United States are in the western states containing the Cascade, San Bernardino, Sierra Nevada, and Rocky Mountain ranges.[1-3]

Consideration of TBRF is critical in patients presenting with recurring fevers. Cardiac and neurologic complications may develop with TBRF, with long-term sequelae that may be permanent. Reviewing a broad differential diagnosis *(Table 1[1,3-6])* for fever when TBRF is suspected will help rule out other possible causes of fever that, if misdiagnosed, could result in significant morbidity or mortality (e.g., Lyme disease, malaria in a returning traveler).

Illustrative Case

A 60-year-old man presented to an emergency department in Boise, Idaho, with a one-month history of intermittent fevers and headaches. The initial fever peaked at 40.6°C (105°F), was accompanied by a headache, lasted for three days, and resolved spontaneously after an episode of shaking chills. The patient had a second fever 13 days later, peaking at 39.4°C (103°F) with diffuse abdominal pain and blurred vision. This fever lasted two days and resolved spontaneously. At the time of the second fever, a family physician assessed the patient. Routine blood tests were normal except an elevated total bilirubin level (6.0 mg per dL) [102.6 mmol per L]. An abdominal computed tomography scan was normal. The patient was referred to an ophthalmologist, who diagnosed iritis.

The patient developed a third fever with headache and visual symptoms 26 days after the initial symptoms, prompting presentation to the emergency department. Past

---

TABLE 1

Differential Diagnosis of Tick-Borne Relapsing Fever

Foreign travel	General infection	Occupational and recreational exposure
Amebic liver abscess	Influenza	Brucellosis
Babesiosis	Meningococcemia	Colorado tick fever
Dengue fever	Salmonellosis	Ehrlichiosis
Leptospirosis	Shigellosis	Lyme borreliosis
Louse-borne relapsing fever		Rat-bite fever
Malaria		Rickettsiosis
Typhoid fever		Tularemia
Viral hepatitis		

Information from references 1 and 3 through 6.

---

medical history and family history were unremarkable. The patient took no medications. He reported traveling to Vietnam four years earlier and Honduras 18 months earlier, and he took malaria prophylaxis for both trips. The patient also had been camping in the Bear Valley region of Idaho. Review of systems was otherwise negative.

On examination, the patient was febrile (39.7°C [103.4°F]), tachycardic (113 beats per minute), and hypertensive (195/107 mm Hg). Other vital signs were stable, and physical examination was normal.

A complete blood count was normal. Manual differential demonstrated 81 percent segmented neutrophils and a low lymphocyte count (6 percent). Total bilirubin was elevated (2.3 mg per dL [39.33 mmol per L]; direct bilirubin, 0.4 mg per dL [6.84 mmol per L]). A reticulocyte count was elevated (3.37 percent). Urinalysis was
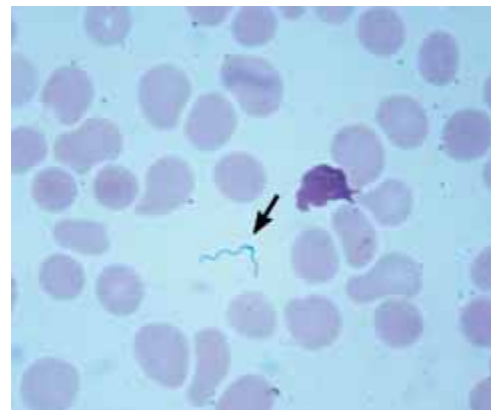

Figure 1. A spirochete *(arrow)* in a thin smear of peripheral blood with Giemsa stain.

positive for protein (1+). Scant spirochetes were detected in a peripheral blood smear prepared with Giemsa stain *(Figure 1)*.

A presumptive diagnosis of Borrelia infection was made, and the patient was admitted and started on tetracycline (500 mg orally, four times daily). The patient's maximum temperature in the hospital was 39.3°C (102.8°F), which returned to normal after 24 hours. Visual symptoms resolved after 24 hours, and he was discharged 36 hours after admission and continued tetracycline for 10 days. Further discussion with the patient revealed that the area where he had been camping had a large squirrel population, though he did not recall being bitten by any insects.

The Authors

CLAY ROSCOE, M.D., is a resident physician at Family Medicine Residency of Idaho in Boise. He received his medical degree from the University of Pennsylvania School of Medicine, Philadelphia.

TED EPPERLY, M.D., is chairman and program director of the Family Medicine Residency of Idaho. He also is clinical professor at the University of Washington School of Medicine in Seattle, where he received his medical degree.

Address correspondence to Clay Roscoe, M.D., Family Medicine Residency of Idaho, 777 N. Raymond St., Boise, ID 38704 (e-mail: clay.roscoe@fmridaho.org). Reprints are not available from the authors.

Epidemiology

More than 450 cases of TBRF were reported between 1977 and 2000 in the United States.[5] The majority of TBRF infections have occurred in Washington state and northern Idaho, with clusters of infections reported in Spokane County, Wash.; Estes Park, Colo.; New Mexico; Montana; and the north rim of the Grand Canyon.[3,7-13]

In North America, most cases of TBRF are associated with two species of Argasidae (soft) ticks, *Ornithodoros hermsii* and *Ornithodoros turicata*. Ornithodoros ticks are obligate blood feeders; they maintain continuous Borrelia infections in salivary gland tissue, and transmit spirochetes when feeding.

O. hermsii is found in the Pacific Northwest and the southwestern United States, and *O. turicata* is found sporadically from Kansas to central Mexico and California. Natural hosts for *O. hermsii* include squir-rels and chipmunks. Hosts for *O. turicata* include cattle, rodents, pigs, snakes, tortoises, and possibly coyotes.

Human infection commonly occurs in the setting of a mountain cabin that has been infested with rodents and *O. hermsii* ticks *(Figure 2)*. When rodents or other natural hosts vacate a cabin, humans may become the only available host. Patients usually are unaware of a tick bite or exposure.[1,2,8] TBRF from *B. turicata*–infected ticks also commonly occurs after humans explore caves or crawl under buildings, and cases have been described in persons who have handled dead rodents.[1,5] Blood feeding by soft-bodied ticks takes less than one hour and usually occurs at night.[1,4]

Pathogenesis

Borrelia spirochetes do not infect blood cells directly, but the severity of TBRF correlates with the number of spirochetes in the

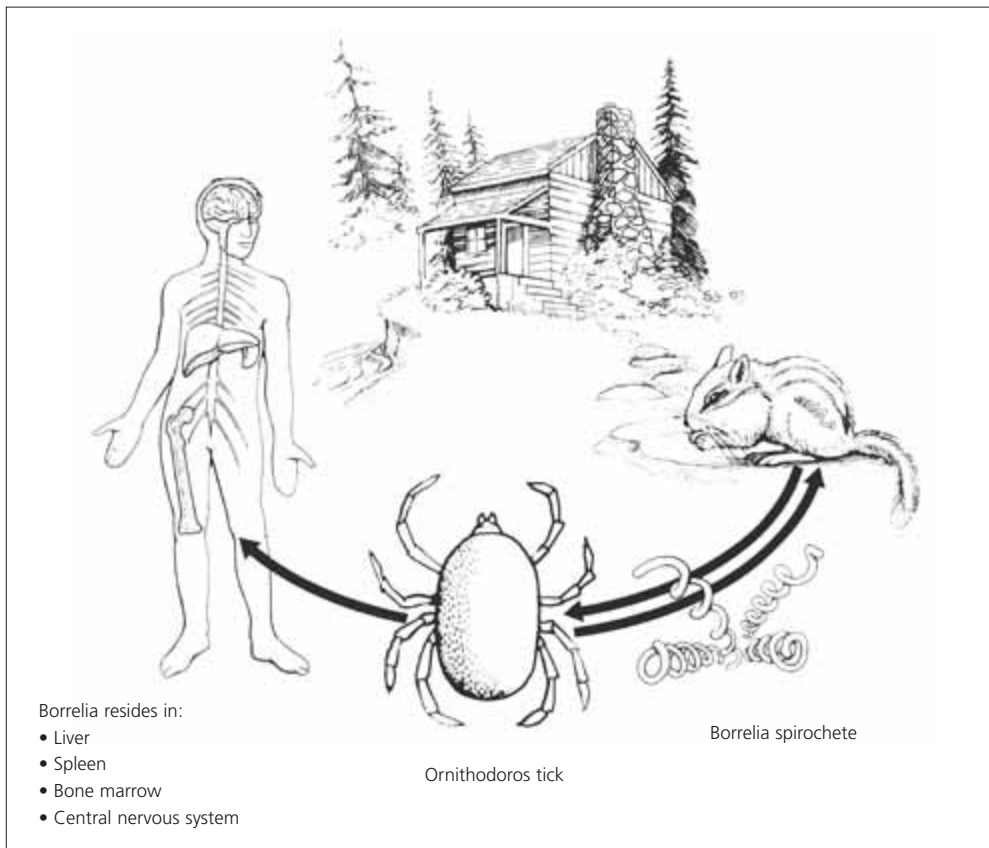Borrelia resides in:
• Liver
• Spleen
• Bone marrow
• Central nervous system

Ornithodoros tick

Borrelia spirochete

ILLUSTRATION BY STEPHEN GRAEPEL

Figure 2. Typical setting for transmission of tick-borne relapsing fever.

> Mild leukocytosis, elevated erythrocyte sedimentation rate, and anemia may be present in patients with tick-borne relapsing fever.

bloodstream. An IgM immune response is capable of clearing one Borrelia serotype, but because of the organism's ability to undergo antigenic variation, several serotypes may be present in the bloodstream at one time. With clearance of one serotype, less common serotypes proliferate, causing the relapsing fever pattern that characterizes TBRF.[4,6,14]

Borrelia spirochetes are capable of moving through or between vascular endothelial cells. During asymptomatic intervals, organisms sequester in the liver, spleen, bone marrow, and the central nervous system (CNS). The immune response may be unsuccessful in clearing Borrelia from the eye, brain, and cerebrospinal fluid (CSF), and relapsing fever spirochetes may persist in these locations for years.[15,16]

Clinical Presentation

TBRF should be considered in patients with recurrent fevers and a history of potential exposure to soft-bodied ticks. Fevers are sudden, high ($\geq$ 39.2°C [$\geq$ 102.5°F]), and are followed by an afebrile period. The first fever lasts three to six days and usually ends with a crisis of rigors, continued fever, hypertension, and tachycardia.[1] Fever crises usually last less than 30 minutes and are followed by diaphoresis, hypotension, and a decreasing temperature. The interval between fevers ranges from four to 14 days.[15]

Headache, arthralgia, myalgia, neck stiffness, and nausea are most common with the initial fever episode (*Table 2*[1]). Neurologic symptoms including delirium, facial palsy, meningismus, and radiculopathy may occur and are more common after the second fever episode.[1,17]

Elevated pulse and blood pressure are common, especially during febrile episodes.[5] Unilateral or bilateral Bell's palsy or deafness from seventh or eighth cranial nerve involvement may be present. Meningitis or meningoencephalitis are serious consequences of TBRF and may result in residual hemiplegia or aphasia. Visual impairment from unilateral or bilateral iridocyclitis or panoph-

thalmitis may be permanent. In contrast, altered mental status and nuchal rigidity not associated with other neurologic symptoms usually are the result of spirochetemia rather than direct CNS infection.[17]

A gallop heard on cardiac auscultation may suggest myocardial involvement; myocarditis is prominent in fatal cases of TBRF.[18] Splenomegaly, often presenting as abdominal or left shoulder pain, is common. Hepatomegaly occurs in approximately 10 percent of patients with TBRF.[5] Infection during pregnancy can lead to a spontaneous abortion or stillbirth. Transplacental transmission of spirochetes and infection at birth is possible. Children and pregnant women

TABLE 2
Common Manifestations of Tick-Borne Relapsing Fever

Sign or symptom	Frequency (%)
Headache	94
Myalgia	92
Chills	88
Nausea	76
Arthralgia	73
Vomiting	71
Abdominal pain	44
Confusion	38
Dry cough	27
Eye pain	26
Diarrhea	25
Dizziness	25
Photophobia	25
Neck pain	24
Rash	18
Dysuria	13
Hepatomegaly	10
Jaundice	10
Splenomegaly	6
Conjunctival injection	5
Eschar	2
Meningitis	2
Nuchal rigidity	2

Adapted with permission from Dworkin MS, Schwan TG, Anderson DE Jr. Tick-borne relapsing fever in North America. Med Clin N Am 2002;86:425.

tend to have a more prolonged and serious disease course.[5,19]

Laboratory Diagnosis

TBRF is diagnosed by detecting spirochetes in thin and thick smears of peripheral blood prepared with Wright's or Giemsa stain or by culture isolations between fever onset and peak.[1,13] Direct and indirect immuno-fluorescence and experimental polymerase chain reaction testing are available in some laboratories.[20-23]

Mild leukocytosis, elevated erythrocyte sedimentation rate, and anemia may be present in patients with TBRF. Thrombocytopenia (i.e., $\geq$ 50,000 platelets per mm^3), elevated serum unconjugated bilirubin levels, elevated aminotransferase levels, prolonged prothrombin and partial thromboplastin times, proteinuria, and microhematuria may be present. A prolonged corrected Q-T interval on electrocardiography may be present in persons with TBRF-induced myocarditis.[3,4,16]

Analysis of CSF is indicated if signs of meningitis or meningoencephalitis are present. Mononuclear pleocytosis, a mildly to moderately elevated protein level, and normal glucose levels in the CSF support the diagnosis of CNS Borrelia infection.[5]

Treatment

The recommended treatment for patients with TBRF is doxycycline (Vibramycin) at a dosage of 100 mg orally, twice daily for seven to 10 days, or tetracycline at a dosage of 500 mg, four times daily for seven to 10 days. When tetracycline is contraindicated (i.e., in children younger than eight years or pregnant women[1]), a macrolide antibiotic may be prescribed (e.g., erythromycin at a dosage of 500 mg orally, four times daily for seven to 10 days).[4,19,24,25] Penicillins are effective but should be given intravenously, especially when CNS involvement is suspected. There is no evidence of antibiotic-resistant TBRF when using the above regimens.[17]

A Jarisch-Herxheimer reaction may occur within two hours of treatment in up to 54 percent of treated patients with TBRF.[1] This reaction is caused by massive cytokine release and manifests as fever, tachycardia, chills, rigors, diaphoresis, and hypotension.[5] Reaction duration usually is less than four hours, but observation should continue for 12 to 24 hours after administration of antibiotics. Jarisch-Herxheimer reactions occur more often after administration of tetracyclines.[17] Cardiovascular collapse and death are rare complications. The use of acetaminophen, corticosteroids, and non-steroidal anti-inflammatory drugs does not modify outcomes significantly.[1]

When patients with TBRF are treated appropriately, the mortality rate is less than 1 percent.[5] Indicators of poor prognosis include myocarditis, stupor or coma, poor hepatic function, and diffuse bleeding.

Prevention

Exposure to TBRF is decreased by rodent-proofing homes and avoiding animal burrows and caves. Spraying buildings with 0.5 percent malathion will reduce tick populations.[4] The home environment also should be free of squirrels and chipmunks, and gloves should be worn when handling dead rodents.

Persons in tick-infected areas should wear pants and long-sleeved shirts and apply insect repellent containing *N,N*-diethyl-*m*-toluamide (DEET) to the skin and clothing, even before going to sleep. All patients with TBRF should be reported to local health departments for surveillance of outbreaks. Persons who hike and camp in endemic areas should perform daily body examinations to ensure that all ticks are promptly removed, and they should seek medical care immediately if signs or symptoms suggestive of TBRF develop.[9]

REFERENCES

1. Dworkin MS, Schwan TG, Anderson DE Jr. Tick-borne relapsing fever in North America. Med Clin North Am 2002;86:417-33.

2. Rawlings JA. An overview of tick-borne relapsing fever with emphasis on outbreaks in Texas. Tex Med 1995;91:56-9.

3. Dworkin MS, Anderson DE Jr, Schwan TG, Shoemaker PC, Banerjee SN, Kassen BO, et al. Tick-borne relapsing fever in the northwestern United States and southwestern Canada. Clin Infect Dis 1998;26:122-31.

4. Horton JM, Blaser MJ. The spectrum of relapsing fever in the Rocky Mountains. Arch Intern Med 1985;145:871-5.

5. Dworkin MS, Shoemaker PC, Fritz CL, Dowell ME, Anderson DE Jr. The epidemiology of tick-borne relapsing fever in the United States. Am J Trop Med Hyg 2002;66:753-8.

6. Barbour AG. Antigenic variation of a relapsing fever Borrelia species. Annu Rev Microbiol 1990;44:155-71.

7. Centers for Disease Control and Prevention. Tickborne relapsing fever outbreak after a family gathering—New Mexico, August 2002. MMWR Morb Mortal Wkly Rep 2002;52:809-12.

8. Goubau PF. Relapsing fevers. A review. Ann Soc Belg Med Trop 1984;64:335-64.

9. Paul WS, Maupin G, Scott-Wright AO, Craven RB, Dennis DT. Outbreak of tick-borne relapsing fever at the north rim of the Grand Canyon: evidence for effectiveness of preventive measures. Am J Trop Med Hyg 2002;66:71-5.

10. Boyer KM, Munford RS, Maupin GO, Pattison CP, Fox MD, Barnes AM, et al. Tick-borne relapsing fever: an interstate outbreak originating at Grand Canyon National Park. Am J Epidemiol 1977;105:469-79.

11. Centers for Disease Control and Prevention. Outbreak of relapsing fever—Grand Canyon National Park, Arizona, 1990. MMWR Morb Mortal Wkly Rep 1991;40:296-7,303.

12. Schwan TG, Policastro PF, Miller Z, Thompson RL, Damrow T, Keirans JE. Tick-borne relapsing fever caused by Borrelia hermsii, Montana. Emerg Infect Dis 2003;9:1151-4.

13. Trevejo RT, Schriefer ME, Gage KL, Safranek TJ, Orloski KA, Pape WJ, et al. An interstate outbreak of tick-borne relapsing fever among vacationers at a Rocky Mountain cabin. Am J Trop Med Hyg 1998;58:743-7.

14. Barbour AG. Immunobiology of relapsing fever. Contrib Microbiol Immunol 1987;8:125-37.

15. Southern PM, Sanford JP. Relapsing fever: a clinical microbiological review. Medicine 1969;48:129-34.

16. Cadavid D, Bundoc V, Barbour AG. Experimental infection of the mouse brain by a relapsing fever Borrelia species: a molecular analysis. J Infect Dis 1993;168:143-51.

17. Cadavid D, Barbour AG. Neuroborreliosis during relapsing fever: review of the clinical manifestations, pathology, and treatment of infections in humans and experimental animals. Clin Infect Dis 1998;26:151-64.

18. Wengrower D, Knobler H, Gillis S, Chajek-Shaul T. Myocarditis in tick-borne relapsing fever. J Infect Dis 1984;149:1033.

19. Jongen VH, van Roosmalen J, Tiems J, Van Holten J, Wetsteyn JC. Tick-borne relapsing fever and pregnancy outcome in rural Tanzania. Acta Obstet Gynecol Scand 1997;76:834-8.

20. Magnarelli LA, Anderson JF, Johnson RC. Cross-reactivity in serological tests for Lyme disease and other spirochetal infections. J Infect Dis 1987;156:183-8.

21. Picken RN. Polymerase chain reaction primers and probes derived from flagellin gene sequences for specific detection of the agents of Lyme disease and North American relapsing fever. J Clin Microbiol 1992;30:99-114.

22. Poulsen LW, Iversen G. Relapsing fever: a differential diagnosis to malaria. Scand J Infect Dis 1996;28:419-20.

23. Suh KN, Kozarsky PE, Keystone JS. Evaluation of fever in the returned traveler. Med Clin North Am 1999;83:997-1017.

24. de Pierpont E, Goubau P, Verhaegen J, Vandepitte J. Single dose minocycline and doxycycline treatment of tick-borne relapsing fever. A double-blind clinical trial in Rwanda. Ann Soc Belg Med Trop 1983;63:357-61.

25. Gilbert DN, Moellering RC, Sande MA. The Sanford Guide to antimicrobial therapy. 35th ed. Hyde Park, Vt.: Antimicrobial Therapy, 2005:39.