

# 76 - 190 Relapsing Fever

## 190 Relapsing Fever

TABLE 189-1 Treatment and Chemoprophylaxis of Leptospirosis in Adults<sup>a</sup>

| INDICATION                    | REGIMEN                                                                                                                                                                       |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Treatment Mild leptospirosis  | Doxycycline <sup>b</sup> (100 mg PO bid) or Amoxicillin (500 mg PO tid) or Ampicillin (500 mg PO tid)                                                                         |
| Moderate/severe leptospirosis | Penicillin (1.5 million units IV or IM q6h) or Ceftriaxone (2 g/d IV) or Cefotaxime (1 g IV q6h) or Doxycycline <sup>b</sup> (loading dose of 200 mg IV, then 100 mg IV q12h) |
| Chemoprophylaxis              | Doxycycline <sup>b</sup> (200 mg PO once a week) or Azithromycin (250 mg PO once or twice a week)                                                                             |

<sup>a</sup>All regimens are given for 7 days. <sup>b</sup>Doxycycline should not be given to pregnant women or children. <sup>c</sup>The efficacy of doxycycline prophylaxis in endemic or epidemic settings remains unclear. Experiments in animal models and a cost-effectiveness model indicate that azithromycin has a number of characteristics that may make it efficacious in treatment and prophylaxis. of major organ-system failure or lessen its severity. Although studies supporting antibiotic therapy have produced conflicting results, clinical trials are difficult to perform in settings patients frequently present for medical care in the later stages of disease. Antibiotics are less likely to benefit patients in whom organ damage has already occurred. Two open-label randomized studies comparing penicillin with parenteral cefotaxime, parenteral ceftriaxone, and doxycycline showed no significant differences among the antibiotics with regard to complications and mortality risk. Thus ceftriaxone, cefotaxime, or doxycycline is a satisfactory alternative to penicillin for the treatment of severe leptospirosis. Antimicrobial susceptibility testing is not routine practice in individual cases of leptospirosis; to date, however, antibiotic resistance has not been reported in isolates from patients or the environment.

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In mild cases, oral treatment with doxycycline, azithromycin, ampicillin, or amoxicillin is recommended. In regions where rickettsial diseases are coendemic, doxycycline or azithromycin is the drug of choice. In rare instances, a Jarisch-Herxheimer reaction develops within hours after the initiation of antimicrobial therapy. Aggressive supportive care for leptospirosis is essential and can be life-saving. Patients with nonoliguric renal dysfunction require aggressive fluid and electrolyte resuscitation to prevent dehydration and precipitation of oliguric renal failure. Peritoneal dialysis or hemodialysis should be provided to patients with oliguric renal failure. Rapid initiation of hemodialysis has been shown to reduce mortality risk and typically is necessary only for short periods. Patients with pulmonary hemorrhage may have reduced pulmonary compliance (as seen in ARDS) and may benefit from mechanical ventilation with low tidal volumes to avoid high ventilation pressures. Evidence is contradictory for the use of glucocorticoids and desmopressin as adjunct therapy for pulmonary involvement associated with severe leptospirosis.

■ ■ **PROGNOSIS** Most patients with leptospirosis recover. However, post-leptospirosis symptoms, mainly of a depression-like nature, may occur and persist for years after the acute disease. Mortality rates are highest among patients who are elderly and those who have severe disease (pulmonary hemorrhage, Weil's syndrome). Leptospirosis during pregnancy is associated with high fetal mortality rates. Long-term follow-up of patients with renal failure and hepatic dysfunction has documented good recovery of both renal

and hepatic function. ■ ■ **PREVENTION** Individuals who may be exposed to *Leptospira* through their occupations or their involvement in recreational freshwater activities should

be informed about the risks. Measures for controlling leptospirosis include avoidance of exposure to urine and tissues from infected animals through proper eyewear, footwear, and other protective equipment. Targeted rodent control strategies have a potential benefit. Vaccines for agricultural and companion animals are generally available, and their use should be encouraged. The veterinary vaccine used in each area should contain the serovars known to be present in that area in order to prevent vaccine serovar mismatch. Unfortunately, some vaccinated animals potentially still excrete leptospires in their urine. Commercial vaccines for human leptospirosis are available in Japan, China, Cuba, and France. These vaccines, made with bacterins— inactivated *Leptospira*—provide short-term, serovar-specific immunity but cause strong adverse side effects; both usability and availability remain problematic. One of the largest-scale trials of vaccine efficacy for leptospirosis in humans has been reported from Cuba. However, no conclusions can be drawn about efficacy and adverse reactions because of insufficient study design and outcome details. The efficacy of chemoprophylaxis with doxycycline (200 mg once a week) or azithromycin (in pregnant women and children) is being disputed, but focused pre- and postexposure administration is indicated in instances of well-defined short-term exposure (Table 189-1). Acknowledgment The authors gratefully acknowledge Dr. Marga G. A. Goris for her substantial contributions to this chapter in previous editions. ■ ■ **FURTHER READING** Adler A: *Leptospira* and Leptospirosis. Berlin Heidelberg, SpringerVerlag, 2015. Azevedo IR et al: Human leptospirosis: In search for a better vaccine. *Scand J Immunol* 98:1, 2023. de Vries SG et al: Leptospirosis among returned travelers: A GeoSentinel Site Survey and Multicenter Analysis—1997–2016. *Am J Trop Med Hyg* 99:127, 2018. Haake DA, Levett PN: Leptospirosis in humans. *Curr Top Microbiol Immunol* 387:65, 2015. Levett PN: Leptospirosis. *Clin Microbiol Rev* 14:296, 2001. Petakh P et al: Current treatment options for leptospirosis: A minireview. *Front Microbiol* 15:1403765, 2024. Sykes JE et al: A global one health perspective on leptospirosis in humans and animals. *J Am Vet Med Assoc* 260:1589, 2022. van Samkar A et al: Suspected leptospiral meningitis in adults: Report of four cases and review of the literature. *Neth J Med* 73:464, 2015. Vincent AT et al: Revisiting the taxonomy and evolution of pathogenicity of the genus *Leptospira* through the prism of genomics. *PLoS Negl Trop Dis* 13:e0007270, 2019. Alan G. Barbour

**Relapsing Fever** Relapsing fever is caused by infection with any of several species of *Borrelia* spirochetes. It occurs in three different clinical and epidemiologic forms: louse-borne relapsing fever (LBRF), soft tick relapsing fever (STRF), and hard tick relapsing fever (HTRF). Physicians in ancient Greece distinguished LBRF from other febrile disorders by its characteristic clinical presentation: two or more fever episodes separated by varying periods of well-being. In the nineteenth century, LBRF was one of the first diseases to be associated with a specific microbe by virtue of its characteristic laboratory finding: the presence of large numbers of spirochetes of the genus *Borrelia* in the blood. The host responds with systemic inflammation that results in an illness ranging from a flulike syndrome to sepsis. Other manifestations

are the consequences of central nervous system (CNS) involvement and disordered hemostasis. Antigenic variation of the spirochetes' surface proteins accounts for the infection's relapsing course. Acquired immunity follows the serial development of antibodies to each of the several variants appearing during an infection. Treatment with antibiotics results in rapid cure but at the

risk of a moderate to severe Jarisch-Herxheimer reaction. LBRF caused large epidemics well into the twentieth century and currently occurs in northeastern Africa and among migrants from that area. At present, however, most cases of relapsing fever are tick-borne in origin, with transmission from either soft-bodied ticks or hard-bodied ticks. Sporadic cases and small outbreaks of STRF are focally distributed on most continents, with Africa and Central Asia most affected. In North America, the majority of reports of relapsing fever have been from the western United States and Canada and northern Mexico. Two other members of the genus, *Borrelia miyamotoi* and *B. lonestari*, are causes of HTRF, an acute febrile illness with nonspecific constitutional symptoms and occasionally meningoencephalitis. ■ ■

**ETIOLOGIC AGENT** Coiled, thin microscopic filaments that swim in one direction and then coil up before heading in another were first observed in the blood of patients with relapsing fever in the 1880s. These microbes were categorized as spirochetes and assigned to the genus *Borrelia*. The breakthrough cultivation medium was rich in ingredients, ranging from simple (e.g., N-acetylglucosamine) to more complex (e.g., serum). The limited biosynthetic capacity of *Borrelia* cells is accounted for by a genome content one-quarter that of *Escherichia coli*. Like other spirochetes, the helix-shaped *Borrelia* cells have two membranes, the outer of which is more loosely secured than in other double-membrane bacteria, such as *E. coli*. As a consequence, fixed organisms with damaged membranes can assume a variety of morphologies in smears and histologic preparations. The flagella of spirochetes run between the two membranes and are not on the cell surface. Although technically gram-negative, the 10- to 20-μm-long *Borrelia* cells, with a diameter of 0.2–0.3 μm, are too narrow to be seen by microscopy of Gram-stained slides. ■

**EPIDEMIOLOGY** *Borrelia recurrentis*, unlike the other relapsing fever *Borrelia* species, is acquired from an insect, the body louse (*Pediculus humanus corporis*), with humans serving as the sole reservoir in its life cycle (Table 190-1). Acquisition occurs not from the bite itself but from either rubbing the crushed insect's hemolymph into the bite site or auto-inoculation into the conjunctivae or a wound. Although LBRF transmission is currently limited to Ethiopia, Eritrea, and Somalia, the disease has had a global

**TABLE 190-1 Relapsing Fever *Borrelia* Species, by RF Type, Geographic Region, and Vector**

| SPECIES                  | RELAPSING FEVER TYPE | REGION(S)                                   | ARTHROPOD VECTOR(S)                                                                        |
|--------------------------|----------------------|---------------------------------------------|--------------------------------------------------------------------------------------------|
| <i>B. crocidurae</i>     | Soft tick RF (STRF)  | West Africa                                 | <i>Ornithodoros sonrai</i>                                                                 |
| <i>B. duttonii</i>       | STRF                 | East Africa, southern and central Africa    | <i>O. moubata</i>                                                                          |
| <i>B. hermsii</i>        | STRF                 | Western North America                       | <i>O. hermsi</i>                                                                           |
| <i>B. hispanica</i>      | STRF                 | North Africa, southern Europe               | <i>O. erraticus</i>                                                                        |
| <i>B. kalaharica</i>     | STRF                 | West Africa, southern Africa                | <i>O. savignyi</i>                                                                         |
| <i>B. lonestari</i>      | Hard tick RF (HTRF)  | Southern and eastern United States          | <i>Amblyomma americanum</i>                                                                |
| <i>B. mazzotti</i>       | STRF                 | Mexico, Central America                     | <i>O. talaje</i>                                                                           |
| <i>B. miyamotoi</i>      | HTRF                 | North America, Asia, Europe                 | <i>Ixodes pacificus</i> , <i>I. persulcatus</i> , <i>I. ricinus</i> , <i>I. scapularis</i> |
| <i>B. nietonii</i>       | STRF                 | Western North America                       | <i>O. hermsii</i>                                                                          |
| <i>B. persica</i>        | STRF                 | Central Asia, Middle East                   | <i>O. tholozani</i>                                                                        |
| <i>B. puertoricensis</i> | STRF                 | Central America                             | <i>O. puertoricensis</i>                                                                   |
| <i>B. recurrentis</i>    | Louse-borne RF       | Africa                                      | <i>Pediculus humanus corporis</i> (human body louse)                                       |
| <i>B. turicatae</i>      | STRF                 | Southwestern United States, northern Mexico | <i>O. turicata</i>                                                                         |
| <i>B. venezuelensis</i>  | STRF                 | Central America, South America              | <i>O. rudis</i>                                                                            |

Although transmission is currently limited to Ethiopia and adjacent countries, *B. recurrentis* infection has had a global distribution in the past, and that potential remains.

**FIGURE 190-1** *Ornithodoros turicata* soft ticks of different ages. distribution in the past, and that potential remains. Outbreaks of LBRF, often in association with typhus, can occur under circumstances of famine, refugee migration, war, homelessness, and incarceration. LBRF can occur in camps of migrants at a distance from their home countries. The several species of *Borrelia* that cause STRF have geographic distributions that correspond with those of their vectors: soft ticks of the genus *Ornithodoros* (Fig. 190-1). STRF is found on most continents but is absent in arctic

environments. For most species, the reservoirs of infection are small to medium-sized mammals, usually rodents, but also pigs and other domestic animals living around human habitats. However, one species, *Borrelia duttonii* in sub-Saharan Africa, is largely maintained by tick transmission between human hosts. In North America, STRF occurs as single cases or small case clusters through transient exposure of persons to tick-infested buildings or caves where mammals have nests or sleep. The two main *Borrelia* species involved in North America are *Borrelia hermsii* and *Borrelia niotonii* in the mountainous west and *Borrelia turicatae* in arid southwestern and south-central regions. The soft tick vectors typically feed for no more than 30 min, usually while the victim is sleeping, and then leave undetected. Transovarial transmission from one generation of ticks to the next means that infection risk may persist in a dwelling long after incriminated mammalian reservoirs have been removed. CHAPTER 190 *Borrelia miyamotoi* is transmitted to humans from other mammals by different species of *Ixodes* hard ticks (e.g., *I. scapularis* in the eastern United States and *I. ricinus* in Europe) that also transmit Lyme disease, babesiosis, anaplasmosis, and a viral encephalitis. *B. miyamotoi* is acquired through outdoor activities and through contact with ticks in forested and shrubby areas during recreation, work, or activities around the home, similarly to Lyme disease (Chap. 191). Among residents of most areas where *B. miyamotoi* and *Borrelia burgdorferi* coexist, the prevalence of antibodies to the former is about one-fourth of that to the latter. In contrast to *B. burgdorferi*, *B. miyamotoi* is transmitted to the host soon after the tick begins to feed, and it may be acquired from tick larvae as well as nymphs and adults. A less common cause of HTRF is *B. lonestari*, which is transmitted by *Amblyomma americanum* ticks of the southern and eastern United States. Relapsing Fever

■ ■ PATHOGENESIS AND IMMUNITY STRF and HTRF spirochetes enter the body in the tick's saliva with the onset of feeding. From an inoculum of a few cells, STRF spirochetes proliferate in the blood, doubling every 6 h to numbers of  $10^6$ – $10^7$ /mL or more. HTRF spirochetes grow more slowly in a mammalian host and attain lower peak concentrations in the blood. *Borrelia* species are extracellular pathogens; their presence inside cells connotes dead bacteria after phagocytosis. Binding of the spirochetes to erythrocytes leads to aggregation of red blood cells, their sequestration in the spleen and liver, and hepatosplenomegaly and anemia. A bleeding disorder is probably the consequence of thrombocytopenia, impaired hepatic production of clotting factors, and/or blockage of small vessels by aggregates of spirochetes, erythrocytes, and platelets. Some species (e.g., *B. turicatae*) are neurotropic and enter the brain, where they are comparatively sheltered from host immunity. Relapsing fever spirochetes can cross the maternal-fetal barrier and cause placental damage and inflammation, leading to intrauterine growth retardation and congenital infection.

Although *Borrelia* species do not have potent exotoxins or a lipopolysaccharide endotoxin, they have abundant lipoproteins that activate Toll-like receptors on host cells, which leads to a proinflammatory process similar to that in endotoxemia, with elevations of tumor necrosis factor  $\alpha$ , interleukin 6, and interleukin 8 concentrations. IgM antibodies specific for the serotype-defining surface lipoprotein appear after a few days of infection and soon reach a concentration that causes lysis of bacteria in the blood through either direct bactericidal action or opsonization. The release of lipoproteins and other bacterial products from dying bacteria provokes a "crisis," during which there can be an increase in temperature, hypotension, and other signs of shock. A similar phenomenon occurring in some patients soon after the initiation of antibiotic treatment is characterized by an abrupt worsening of the patient's condition, which is called a Jarisch-Herxheimer reaction (JHR). PART 5 Infectious Diseases ■ ■ CLINICAL MANIFESTATIONS STRF and

LBRF present with the sudden onset of fever. Febrile periods are punctuated by intervening afebrile periods of a few days; this pattern occurs at least twice in STRF. The patient's temperature is  $\geq 39^{\circ}\text{C}$  and may be as high as  $43^{\circ}\text{C}$ . The first fever episode often ends in a crisis lasting ~15–30 min and consisting of rigors, a further elevation in temperature, and increases in pulse and blood pressure. The crisis phase is followed by profuse diaphoresis, falling temperature, and hypotension, which usually persist for several hours. In LBRF, the first episode of fever is unremitting for 3–6 days; it is usually followed by a single milder episode. In STRF, multiple febrile periods last 1–3 days each. In both forms, the interval between fevers ranges from 4 to 14 days, sometimes with symptoms of malaise and fatigue. The symptoms that accompany the fevers are usually nonspecific. Headache, neck stiffness, arthralgia, myalgia, and vomiting may accompany the first and subsequent febrile episodes. An enlarging spleen and liver cause abdominal pain. A nonproductive cough is common during LBRF and—in combination with fever and myalgias—may suggest influenza. Acute respiratory distress syndrome may occur during LBRF or STRF. On physical examination, the patient with LBRF or STRF may be delirious or apathetic. There may be body lice in the patient's clothes or signs of insect bites. In regions with *B. miyamotoi* or *B. lonestari* infection, a hard tick may be embedded in the skin. Jaundice, epistaxis, and subconjunctival hemorrhages are common during LBRF but not in STRF or HTRF. Splenomegaly or spleen tenderness is common in LBRF and STRF. Localizing neurologic findings are more common in STRF than in LBRF or HTRF. In North America, *B. turicatae* infection has neurologic manifestations, including aseptic meningitis and cranial neuritis, more often than *B. hermsii* or *B. nielsonii* infection. Unilateral or bilateral Bell's palsy is the most common form of cranial neuritis and typically presents in the second or third febrile episode, not the first. Visual impairment from unilateral or bilateral iridocyclitis or panophthalmitis may be permanent. In LBRF, neurologic manifestations such as altered mental state are thought to be secondary to systemic inflammation or small hemorrhages in the brain rather than to direct invasion of the nervous system.

Myocarditis in STRF or LBRF is evidenced by gallops on cardiac auscultation, a prolonged QTc interval, and cardiomegaly and pulmonary edema on chest radiography. General laboratory studies in all forms of relapsing fever are not specific. Mild to moderate normocytic anemia is common, but frank hemolysis and hemoglobinuria do not develop. Leukocyte counts range from slightly elevated to leukopenic. Mild to moderate thrombocytopenia is common; platelet counts may fall below  $50,000/\mu\text{L}$  in some cases. C-reactive protein and procalcitonin levels are elevated. Laboratory evidence of hepatitis can be found, with elevated serum concentrations of aminotransferases; the prothrombin and partial thromboplastin times may be moderately prolonged. Analysis of the cerebrospinal fluid (CSF) is indicated in all cases of suspected relapsing fever with signs of meningitis or meningoencephalitis. The presence of mononuclear pleocytosis and mildly to moderately elevated protein levels justifies intravenous antibiotic therapy in relapsing fever. The manifestations and course of *B. miyamotoi* disease are not as distinctive as those of relapsing fever. The most common presentation is acute onset of fever with chills, headache, and myalgias starting 1–2 weeks after a tick bite. Patients have been hospitalized with a presumptive diagnosis of undifferentiated sepsis. There may be a second fever episode in untreated patients. Meningoencephalitis or meningitis was documented in adults with deficiencies in humoral immunity, including the effects of anti-B cell antibodies such as rituximab. If the patient has coexisting early Lyme disease, there may be erythema migrans, the localized skin rash. ■

■ **DIAGNOSIS** STRF or LBRF should be considered in a patient with the characteristic fever pattern and a history of recent exposure—i.e., within 1–2 weeks before illness onset—to body lice or soft

ticks in geographic areas with documented current or past transmission. Because of the longevity of the ticks and the transovarial transmission of the pathogen in the ticks, a case of relapsing fever may be diagnosed many years after the last case reported in that locale. The lice may be on the clothes of a migrant, refugee, or unhoused person. While the epidemiologic risks for *B. miyamotoi* HTRF are similar to those for Lyme disease, prompt removal of an embedded tick upon discovery may not reduce the risk of infection of this pathogen. The bedrock for laboratory diagnosis of LBRF and STRF remains direct detection of the spirochetes by microscopy of the blood. Manual differential counts of white blood cells by Wright, Giemsa, or GiemsaWright stain usually reveal spirochetes in thin blood smears if their concentration is  $\geq 105/\text{mL}$  and several oil-immersion fields are examined (Fig. 190-2). The peak density of *B. miyamotoi* or *B. lonestari* in the blood may not be high enough for use of a blood smear alone for diagnosis. For LBRF and STRF, the preferred time to obtain a blood specimen is at or just before fever's peak. Lower concentrations of spirochetes may be revealed by a thick blood smear that is treated with 0.5% acetic acid before staining. An alternative is a wet mount of citrated blood mixed with saline and examined by phase-contrast or dark-field microscopy for motile spirochetes. Polymerase chain reaction (PCR) and similar nucleic acid amplification test (NAAT) procedures are increasingly used for examination of blood or CSF in cases of suspected relapsing fever. Overall, NAAT is more sensitive than thin blood smear, particularly for samples obtained between febrile episodes. PCR is the preferred procedure for direct detection of *B. miyamotoi* or *B. lonestari* in blood or CSF. Culture of blood or CSF in Barbour-Stoenner-Kelly broth medium or equivalent is an option for isolation of *Borrelia* species. However, visible growth takes several days, and few laboratories offer this service. Options for serologic confirmation of infection are limited, and results may be misleading. Whole cell-based assays, such as enzyme-linked immunosorbent assay (ELISA) and the C6 peptide ELISA for Lyme disease, may be positive in relapsing fever through antigenic cross-reactivities among these spirochetes. A commercially available assay based on GlpQ—a protein antigen of STRF, HTRF, and LBRF *Borrelia* species but not of any Lyme disease species—has better

FIGURE 190-2 Photomicrograph of tick-borne relapsing fever spirochete (*Borrelia turicatae*) in a Giemsa-Wright-stained thin blood smear. Included in the figure are a polymorphonuclear leukocyte and two platelets. specificity but commonly is negative at a time when a blood smear or PCR assay would be positive. The results of a GlpQ-based assay or an indirect immunofluorescence assay of whole cells cannot be used to differentiate between different *Borrelia* species as to etiology. A positive IgG immunoassay of a single specimen may be the consequence of a past infection and not the present illness. ■ ■

**DIFFERENTIAL DIAGNOSIS** Depending on the patient's history of residential, occupational, travel, and recreational exposures, the differential diagnosis of STRF includes one or more of the following infections that feature either periodicity in Tick-borne relapsing fever Louse-borne relapsing fever Meningitis/encephalitis Oral therapy Sequential therapy Intravenous ceftriaxone 2 g qd or Na penicillin G, 5 million U q6h for 14 days First choice Age  $\geq 9$  years, not pregnant: doxycycline, 100 mg bid Age  $< 9$  years: erythromycin, 12.5 mg/kg per day Second choice Age  $\geq 9$  years, not pregnant: tetracycline 500 mg qid Third choice Age  $\geq 9$  years: erythromycin, 500 mg qid Duration: 10 days

FIGURE 190-3 Algorithm for treatment of relapsing fever. If it is not known whether the patient has tick-borne or louse-borne relapsing fever, the patient should be treated for the tick-borne form. The dashed line indicates that central nervous system invasion in louse-borne relapsing fever is uncommon.

the fever pattern or an extended single febrile period with nonspecific constitutional symptoms: Rocky Mountain spotted fever and other rickettsioses, ehrlichiosis, anaplasmosis, tick-borne viral infection, and babesiosis in North America, Europe, Russia, and northeastern Asia. STRF with Bell's palsy may be misdiagnosed as Lyme disease in areas endemic for both diseases. Elsewhere in the Americas and Asia and in most of Africa, malaria, typhoid fever, typhus and other rickettsioses, dengue, and leptospirosis also may be considered. Other agents transmitted by the body louse are *Rickettsia prowazekii*, the cause of typhus, and *Bartonella quintana*, the cause of trench fever. There may be co-infections of malaria, typhus, or typhoid with STRF or LBRF.

B. *miyamotoi* infection may coexist with Lyme disease.

**TREATMENT** Relapsing Fever Penicillin and tetracyclines have been the antibiotics of choice for LBRF and STRF for several decades. Erythromycin has been a long-standing alternative choice. There is no evidence of acquired resistance to these antibiotics. *Borrelia* species are also susceptible to second- and third-generation cephalosporins. These spirochetes are relatively resistant to rifampin, sulfonamides, and aminoglycosides. Spirochetes are no longer detectable in the blood within a few hours after the first dose of an effective antibiotic. Under conditions of limited resources or in the midst of an epidemic, a single dose of antibiotic usually suffices for successful treatment of LBRF (Fig. 190-3). For adults, a single dose of oral doxycycline (200 mg), oral tetracycline (500 mg), or intramuscular ceftriaxone 250 mg for adults and 125 mg for children is effective. The corresponding doses for children are oral tetracycline at 12.5 mg/kg, oral doxycycline at 5 mg/kg, and intramuscular penicillin G procaine at 200,000–400,000 units. When an adult patient is stuporous or nauseated, the intravenous dose of tetracycline is 250–500 mg. Tetracyclines are contraindicated in pregnant and nursing women; for individuals in these groups who are allergic to penicillin, oral erythromycin (500 mg for adults and 12.5 mg/kg for children) is an alternative. While there is little reported experience with other macrolides, such as azithromycin, these are likely to be as effective as erythromycin.

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First choice Single dose of penicillin G ceftriaxone IM 250 mg adults and 125 mg children 800,000 U adults 200,000–400,000 U children then (4–12 h later) Age  $\geq 9$  years, not pregnant: doxycycline, 100 mg bid or tetracycline 500 mg qid Age  $< 9$  years or pregnant: erythromycin, 12.5 mg/kg per day or 500 mg qid Duration: 7 days Second choice (penicillin allergy): erythromycin, 500 mg qid  $\geq 9$  years or 12.5 mg/kg per day  $< 9$  years Duration: 7 days

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