

## Treatment of Lyme Borreliosis

The increasing number of cases of Lyme disease has resulted in frequent questions about the prevention, diagnosis, and treatment of this disease. The following information and guidelines may be helpful.

### EPIDEMIOLOGIC CONSIDERATIONS

Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi*. The organism is carried by a small tick, usually nymphal *Ixodes dammini* on the East Coast and *Ixodes pacificus* in the West. The disease is clustered in specific areas, with most cases reported in the Northeast, Wisconsin, Minnesota, and California. For patients who do not live in or have not traveled in those areas, the chances of acquiring Lyme disease are very small. However, at least some endemic cases have been reported from 46 states and Canada. Dogs can be infected with this spirochete and can develop symptoms of arthritis.

### PREVENTION

Tick bites can be decreased by wearing clothing with long sleeves and long pants. Permethrin sprayed on clothing is effective in decreasing tick attachment. Tick repellents such as DEET are effective, but they require repeated application every 1 to 2 hours,<sup>1</sup> and they have some negative side effects. For example, seizures have been reported coincidentally with the application of DEET.<sup>2</sup> If used, DEET should be applied sparingly only to exposed skin and should not be used on children's faces or hands. It should not be applied to irritated or abraded skin and should be washed off after coming indoors.

Daily inspection and prompt removal of ticks should help prevent infection because prolonged

attachment appears to be required for an infected tick to transmit spirochetes. One study in hamsters and mice showed that Lyme disease infection was very rare (1 in 14 cases) when a tick was attached for less than 24 hours. At least 48 hours of feeding were required to infect half of the test animals, and most animals were infected only after 72 hours (13 in 14 cases).<sup>3</sup>

A tick should be removed by grasping it with a fine tweezer close to the skin and pulling gently. Care should be taken to avoid squeezing the body of the tick.

The low transmission rate of *B burgdorferi* in animal studies indicates that antibiotic prophylaxis of children is not indicated following a tick bite, even in an endemic area. In addition, in the only published study, minimal benefit was documented. In the study done in Connecticut (an endemic area) of 56 patients who had been bitten by ticks, 29 were treated with oral penicillin and 27 received no antibiotics. Ticks were available for study from 21 patients, and although 6 (29%) tested positive for *B burgdorferi*, only one untreated patient developed Lyme disease.<sup>4</sup>

### DISEASE

Early disease is manifested by fever, malaise, headache, mild neck stiffness, arthralgia, and a distinctive skin rash characterized by a red macule or papule, which expands to a red-bordered lesion with central clearing. Occasionally the central area may become necrotic. About 60% to 80% of those infected have erythema migrans. Later disease entities include arthritis; cardiac involvement; and neurologic disease with cranial nerve palsies, aseptic meningitis, and peripheral radiculoneuropathy.<sup>5,6</sup> Some school-age children with Lyme disease have manifested a decline in academic achievement accompanied by poor memory and behavioral changes.<sup>7</sup>

### PREGNANCY

*B burgdorferi* infection during pregnancy can cause infection of the fetus. Two infants of mothers

The recommendations in this publication do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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infected during the first trimester died in the first week of life.<sup>8,9</sup> Autopsy disclosed spirochetes in a variety of tissues, although they were not identified conclusively as *B. burgdorferi*. A study of cord bloods in endemic and nonendemic areas showed no association of Lyme antibodies with congenital abnormalities and no infants with IgM-specific antibodies for the spirochete.<sup>10</sup> Another study of 19 pregnancies in which the mothers were infected with Lyme disease showed five babies with abnormalities, but all the abnormalities were different, and no pattern could be detected.<sup>11</sup> If Lyme disease is capable of producing an abnormality in the fetus, it is probably a rare occurrence.

## DIAGNOSIS

Diagnosis can be made clinically in the early stage if the typical skin rash of erythema chronicum migrans is present. In patients without a rash or who manifest a later disease stage, the diagnosis usually is made by serology.<sup>12</sup> Antibodies may be absent in the first 2 to 3 weeks following infection and may be aborted by antibiotic therapy given early in the disease. Most untreated patients with late-stage disease have a positive antibody titer. Both an indirect fluorescent antibody and an enzyme-linked immunosorbent assay test are available, although enzyme-linked immunosorbent assay is used more widely because it is more sensitive and more specific. However, serologic tests are not yet standardized, and results vary depending on the laboratory. Both false-negative and false-positive results occur. Specificity is lowered by a cross-reaction of *B. burgdorferi* antibody with those against *Treponema pallidum*. However, patients with Lyme disease do not have a positive rapid plasma reagin or Venereal Disease Research Laboratory test. The serological tests currently available utilize the entire organism as an antigen. More specificity may be obtained using more refined tests that are still experimental.

## THERAPY

### In Vitro Antibiotic Activity

In vitro studies of antibiotic sensitivity are difficult to interpret because the organism is very slow growing and varying methods were used in different studies. Most studies compared various tetracyclines with penicillin and erythromycin.<sup>13-15</sup> Some studies tested ceftriaxone and ampicillin. All of the tetracyclines are effective with minimum inhibitory concentration values of 0.2 and 2.0 mg/L; ceftriaxone (0.01 to 1.0 mg/L), ampicillin (0.25 to 1.0 mg/L), penicillin G (0.005 to 8.0 mg/L), and erythro-

mycin (0.91 to 1.0 mg/L) are also effective. The spirochete of Lyme disease is not as susceptible to penicillin as are many other spirochetes.

## Clinical Studies

Even before the causative organism was identified, extensive experience showed that early Lyme disease responded to treatment with oral tetracycline, penicillin G, or erythromycin. In one study, the rash resolved in 5.4 days in patients treated with penicillin G, 5.7 days in those who received tetracycline, and 9.2 days in patients treated with erythromycin.<sup>16</sup> About 50% of the patients had some minor late symptoms of headache, lethargy, or musculoskeletal pain following any of these treatments. Major late complications were not seen in any of the 88 patients treated with tetracycline but were present on follow-up of 3 of the 40 patients who received penicillin and 4 of the 29 patients who received erythromycin therapy.

Multiple skin lesions occur in as many as 50% of patients, representing an immunologic phenomenon and not multiple bites. Some experts feel that patients with this manifestation should receive a longer (30-day) course of therapy. Other experts believe that the length of therapy should be decided by the time required for symptoms to resolve.

Arthritis frequently responds to treatment with oral penicillin, amoxicillin, or tetracycline for 30 days.<sup>17</sup> Some, but not all, patients who fail to respond to oral antibiotics improve with intravenous therapy with penicillin or ceftriaxone. Certain genetically disposed individuals appear to have an immune response that mediates the inflammation in the joint tissues. These patients may not respond to any antibiotic. Steere et al<sup>18</sup> demonstrated a complete resolution of arthritis in 7 of 20 patients treated with 2.4 million units of benzathine penicillin G weekly for 3 weeks. Eleven of 20 patients who received 20 million units of aqueous crystalline penicillin G IV for 10 days had resolution of disease. Further studies are needed to determine the correct therapy for Lyme arthritis that does not respond to oral antibiotics and to determine if children and adults differ in their responses to treatment.

Patients with Lyme carditis can have a myocarditis or complete heart block, but the most common manifestation is a fluctuating atrioventricular block. Mild carditis with first degree heart block, PR interval less than 0.30 seconds, and no significant symptoms can be treated with oral antibiotics, but more severe degrees of heart block usually are treated with parenteral penicillin or ceftriaxone.

Steere et al<sup>18</sup> reported the efficacy of high-dose intravenous aqueous crystalline penicillin G in pa-

tients with neurologic abnormalities secondary to Lyme disease. Twelve patients were treated with 20 million units of penicillin G IV daily for 10 days. Headache, stiff neck, and radicular pain improved by the second day and disappeared in 7 to 10 days, although 5 patients continued to have intermittent headaches for several days. Recovery of motor deficits occurred in 7 to 8 weeks. Three patients continued to have frequent problems with arthralgia, musculoskeletal pain, and fatigue.

Dattwyler et al treated 23 adults with chronic neurologic and arthritic problems caused by Lyme disease with either high-dose intravenous penicillin or ceftriaxone.<sup>19</sup> Improvement was gradual and little immediate effect was seen during treatment.

No studies have been reported on the use of ceftriaxone in children for treatment of the late complications of Lyme disease. However, a dose of 75 to 100 mg/kg per day, with a maximum dose of 2 g/d, appears appropriate.

The Jarisch-Herxheimer reaction with chills, malaise, fever, pain, or anaphylaxis may be seen when therapy is started.

The most appropriate therapy for Lyme disease during pregnancy has not yet been determined.

## RECOMMENDATIONS

The following recommendations are based on empiric clinical information, because studies comparing different duration and doses of therapy have not been performed.

1. If a tick-infested area is entered, clothing should cover as much of the arms and legs as possible. Permethrin can be sprayed on the clothing. Tick repellents must be applied frequently to be effective. DEET should be used sparingly.
2. Daily inspection of family members and pets, with prompt removal of any ticks found, is recommended strongly.
3. Empiric treatment of asymptomatic patients who have been bitten by ticks is not justified.
4. Treatment of early-stage Lyme disease (Table): Tetracycline 250 mg, four times a day, doxycycline, 100 mg twice daily, or amoxicillin, 500 mg three times daily, for 10 to 30 days are the treatments of choice in patients who are 9 years of age or older. Younger children should receive penicillin V or amoxicillin, 1 to 2 g daily or 25 to 50 mg/kg per day in divided doses. Length of therapy depends on manifestations and clinical response. A patient with early-stage disease should be seen after a 14-day course of antibiotic therapy. If all symptoms have resolved, no further therapy is indicated. If symptoms persist, continued therapy is necessary until they have

**TABLE.** Recommended Treatment for Lyme Disease in Children

Early Disease	Drug Dose*
>9 years old	
Tetracycline†	250 mg qid
Doxycycline†	100 mg bid
<9 years old	
Penicillin V	25–50 mg/kg·d divided tid (1–2 g/d)
Amoxicillin	25–50 mg/kg·d divided tid (1–2 g/d)
Late Disease	Drug Dose
Isolated Bell's palsy	Above oral regimen
Arthritis	Above oral regimen
Mild carditis	Above oral regimen
Persistent arthritis	Ceftriaxone 75–100 mg/kg once daily, or penicillin G 300 000 U/kg·d
Severe carditis	Ceftriaxone 75–100 mg/kg once daily, or penicillin G 300 000 U/kg·d
Meningitis or encephalitis	Ceftriaxone 75–100 mg/kg once daily

\* Oral regimens should be continued for 10 to 30 days; parenteral therapy for 14 to 21 days. qid, four times daily; bid, twice daily; tid, three times daily

† Not recommended for children younger than 9 years of age.

resolved. Relapses can occur, requiring re-treatment with the same or other antibiotics. Erythromycin, 30 mg/kg per day in divided doses or 250 mg three times a day, is an acceptable alternative for the penicillin-allergic patient, although it may be less effective.

5. Treatment of late-stage Lyme disease: Isolated seventh nerve palsy with normal cerebrospinal fluid findings, mild carditis, or arthritis can be treated with one of the oral regimens recommended for early-stage disease. Severe carditis, persistent arthritis, or neurologic involvement should be treated with parenteral antibiotics. Although data are limited, ceftriaxone, 75 to 100 mg/kg per day (maximum 2 g/d), is probably the treatment of choice for central nervous system disease. Penicillin G, 300 000 U/kg per day, maximum of 20 million U/d divided every 4 hours, or ceftriaxone can be used for severe carditis or persistent arthritis.

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