Connecticut Medicine

The Journal of the Connecticut State Medical Society

VOLUME 56 JULY 1992 NUMBER 7

CONNECTICUT MEDICINE (ISSN 0010-6178), published monthly at 160 St. Ronan St., New Haven, CT 06511
Subscription rate included in membership dues. Non-members: $25.00 per year. Second-class postage paid at New Haven, CT
POSTMASTER: Send address changes to 160 St. Ronan St., New Haven, CT 06511

Clinical Manifestations and Antibiotic Treatment of Lyme Disease

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ABSTRACT—As the incidence of Lyme disease increases in Connecticut and world-wide, considerable attention has been given to its prompt diagnosis and treatment. Creating further interest in this infection is the awareness that inappropriate therapy may result in significant disabling sequelae many years later. In this review, we focus mainly on current treatment options, but stress that the recommendations may change appreciably, as more information appears on the efficacy of new antibiotics.

Introduction

LYME disease, named for Lyme, Connecticut, where it was first described in the 1970s, is currently the most commonly reported tick borne disease in the United States. Prompted by several young mothers who noted an epidemic of "juvenile rheumatoid arthritis" in their community, an intensive etiologic and epidemiologic investigation of Lyme disease was undertaken by Steere, et al.[1] Their findings showed that skin lesions characteristic of Lyme disease were similar to those previously reported in Europe. The sheep tick, *Ixodes ricinus*, had been identified as the causative agent for the European skin rashes. These findings led to a study of Connecticut ticks, and resulted in the identification of a deer tick, *Ixodes dammini*, as the vector responsible for transmission of Lyme disease.[2] In 1982, Willie Burgdorfer isolated a spirochete from ticks collected on Shelter Island and showed that infection of rabbits with the organism produced the characteristic skin rash of Lyme disease.[3] The organism was named *Borrelia burgdorferi* in his honor.

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During 1985, the incidence of Lyme disease in Connecticut was 22 cases per 100,000 residents. By 1988, 43 states in this country had reported Lyme disease.[4] Recently, Lyme disease has reached epidemic proportions in many areas of the United States and many cases have also been reported worldwide.

Regardless of age or gender, persons at risk of contracting Lyme disease include anyone who frequents the deer tick's woodland habitat. Risk of spirochete transmission increases with the duration of attachment after tick bite.[5] It may in fact require at least 24 hours of contact for infection to occur. During its aggressive nymph stage, the tick usually transmits the disease during the months of May through July. The adult tick, however, can also transmit disease during the spring or fall.[6]

Clinical Manifestations and Pathogenesis

Depending on the stage, Lyme disease can be manifested by dermatologic, cardiac, neurologic, or musculoskeletal symptoms. Prior to the use of antibiotics for the treatment of Lyme disease, infection took the following route: erythema chronica migrans (ECM) was sometimes followed after weeks or months by meningitis or Bell's palsy, and then months or years later by arthritis and/or chronic neurologic manifestations.[6] It has been recognized that each organ system may be affected in either early or late stages of the illness. No one patient necessarily manifests every aspect of the disease; furthermore, the duration of involvement may vary. When considering the diagnosis it is important to note that the clinical signs and symptoms of Lyme disease may occur at any time throughout the year.

Early Stage Disease

The early stage of Lyme disease generally is characterized by the presence of ECM, which usually first appears at the site of the tick bite. Satellite lesions may appear anywhere on the body. However, only 60-80% of Lyme disease patients develop ECM and in addition, only 30% of patients will recall a tick bite.[6] If early treatment is not administered, the spirochete released from the tick

bite will spread throughout the body. Within days or weeks after exposure to the spirochete, symptoms may occur including fever, chills, body aches, fatigue, and stiffness. Approximately 15-20% of untreated patients develop neurologic abnormalities such as cranial neuropathies.[6] The facial paralysis, or Bell's palsy, remains the most common neurologic manifestation of early disseminated Lyme disease, which resolves gradually with or without antibiotic therapy. Other peripheral nervous system disorders associated with Lyme disease include sensory and/or motor nerve dysfunction.[7,8]

At a mean of six months after onset of the disease, approximately 60% of untreated patients have brief attacks of arthritis affecting a large joint.[6] Arthritis may or may not subside spontaneously over a few months, and has been noted to recur over several years. Cardiac involvement, another symptom of early-stage disease, occurs in 4-8% of patients and is associated with a partial heart block that may progress to complete heartblock in some cases.[6]

Late Stage Disease

This stage of Lyme disease is associated with chronic neurologic disease and/or chronic arthritis, both of which may linger for months or years. In addition, the initial symptoms of disease may progress insidiously. For example, ECM may develop to acrodermatitis chronic atrophicans, characterized by atrophy and sclerosis of the skin. The chronic arthritis associated with late-stage disease may result in synovitis, cartilage and bone erosion, and occasionally joint destruction.[6] Early neurologic disorders may include chronic encephalomyelitis, causing spastic paraparesis, bladder dysfunction, organic brain syndrome, and in some cases, demyelinating disease.[8]

Diagnosis

Although the spirochete has been isolated from skin, CSF, or synovial tissue in patients with Lyme disease, cultures are seldom used to make the diagnosis; diagnosis is made by clinical assessment and serologic testing.

In early-stage Lyme disease (ECM), there is really no need to resort to laboratory testing. In fact, serologic tests are often negative in patients with ECM.[6] In late-stage disease, the majority of previously untreated patients will have clearly elevated antibody titers as measured by the enzyme-linked immunosobent assay (ELISA), or indirect assay.

Unfortunately, many laboratories are performing enzyme serologic testing with little regard to quality control or reproducibility of results. Thus, false-negatives and false-positive results are common.[9,10,11] This has led to numerous cases of what we would term "pseudo-Lyme" disease. They are generally patients with nonspecific symptoms (ie, chronic fatigue) with low positive Lyme titers. Unfortunately, many of these patients have persuaded their physicians to give them prolonged courses of antibiotic therapy for their "pseudo-Lyme" disease. For example, of the first 100 patients seen at a Lyme clinic in a major university, only 37 actually had proven Lyme disease, yet most patients had received prolonged courses of antibiotics.[12] Finally, even a true-positive Lyme serology is not necessarily indicative of active Lyme disease. Kaell et al,[13] recently reported four patients with bacterial endocarditis (presenting with fever, malaise, and arthralgias) who had been inappropriately treated for Lyme disease on the basis of positive serologies.

Microbiology

Despite the success of penicillin therapy, the spirochete *Borrellia burgdorferi* is far less sensitive in-vitro to this antibiotic than *Treponema pallidum*. In vitro, ceftriaxone, cefotaxime, tetracycline, and erythromycin are far more active than penicillin G.[14] Ceftriaxone and tetracycline also perform well in the in vivo hamster model while penicillin fares poorly.[14] Further, erythromycin's excellent in vitro activity does not translate into therapeutic efficacy in the animal model.[14,15] This is not a problem shared by the new experimental agent, azithromycin, which is the most active agent tested in borrelia infections in animals.[15] Since this new antibiotic has an extremely long half-life, superb tissue levels, and high activity against *Borrelia burgdorferi*, clinical testing of this agent in human Lyme disease is being eagerly anticipated.

Treatment of Early Disease

More than a decade ago, Steere and coworkers demonstrated more rapid healing of ECM in patients treated with low-dose penicillin or tetracycline than in untreated patients. The numbers who developed neurologic or cardiac abnormalities was small; however, "the frequency of these complications was similar regardless of treatment."[16] Thirty-five percent of penicillin-treated patients still developed arthritis although these results were superior to those in placebo-treated patients. Further studies have also demonstrated the failure of low-dose tetracycline (250 mg four times daily for 10 days) in preventing subsequent arthritis.[17]

Recently, Dattwyler et al, reported that doxycycline 100 mg twice a day or amoxicillin 500 mg with probenecid 500 mg three times a day were equally effective in the treatment of ECM.[18] Post-treatment follow-up at six months showed that none of the patients had symptoms requiring further therapy.

Currently, in nonpregnant adults, doxycycline at a dose of 100 mg twice daily for at least three weeks generally is the recommended therapy. Doxycycline is preferred over tetracycline because of its longer half-life and favorable tissue penetration. In young children and pregnant women, the preferred drug now would be amoxicillin in

doses up to 2 g daily with or without probenecid for at least three weeks. Amoxicillin is thought to be superior to penicillin therapy because of its longer half-life and higher serum and tissue levels. The use of low-dose penicillin (250 mg orally four times daily) can no longer be recommended as optimal therapy for ECM.

Prophylaxis After Tick Bite

A common clinical problem is whether to give prophylactic antibiotic therapy to patients who present having found a deer tick on their body. Currently the risk of Lyme disease appears to be much lower in these patients than was previously thought, since they usually have had tick contact for only a few hours. One randomized study showed that the risk of developing Lyme disease without treatment was similar to the risk of developing an adverse drug reaction.[19] We would therefore advocate prophylactic therapy only in patients who believe that the tick was attached for more than 24 hours, since this would be the highest risk group.

Treatment of Cardiac Disease

The optimal treatment of cardiac disease has not been rigorously studied since there have been so few cases. Minor cardiac disturbances (first degree AV block) should be treated with regimens similar to that employed in ECM. Patients with complete heart block may benefit from initial therapy with high-dose penicillin, ceftriaxone, or cefotaxime for a period of two weeks. Rarely, a temporary pacemaker may be required, but a full recovery is the rule even without antibiotic therapy.[6]

Treatment of Arthritis

Early studies by Steere et al indicated that established Lyme arthritis could be treated with three weeks of intramuscular benzathine penicillin (a regimen similar to that used for late syphilis).[20] However, the response rate was only 35%. High-dose intravenous penicillin yielded more responders but still had a 45% failure rate.[20] A one-month course of doxycycline 100 mg twice daily or amoxicillin/probenecid both 500 mg four times daily will give response rates of 72% and 61% respectively in patients with established Lyme arthritis.[21] Since the amoxicillin/probenecid regimen had more side effects, oral doxycycline therapy is considered to be the initial treatment of choice.

Patients who fail oral therapy for established arthritis may respond to a course of a parenteral third-generation cephalosporin. Dattwyler et al in 1987 reported five patients with large joint arthritis that had failed penicillin therapy but subsequently responded to a two-week course of ceftriaxone.[22] Later this same group reported a randomized trial comparing penicillin with ceftriaxone in late Lyme disease.[23] Five of seven patients in the penicillin group continue to have arthritis while all nine patients receiving ceftriaxone had alleviation of their arthritis. In addition, of the four penicillin nonresponders who were treated with ceftriaxone, all symptoms resolved in three of them. In a study by Hassler et al comparing 3 g of cefotaxime every 12 hours with 20 million units of penicillin per day, each for 10 days, seven of 16 patients with recurrent arthritis were cured in the cefotaxime group vs only four of 18 in the penicillin group.[24]

On the other hand, in a recent study by Liu et al of patients with arthritis who were not helped by one month of appropriate oral antibiotic therapy, only five of 14 high-dose intravenous penicillin treated patients vs six of 15 intravenous ceftriaxone treated patients (not significant) responded.[21] It is possible that patients whose arthritis does not respond to prolonged antibiotic therapy may have an immune basis for their arthritis, and may not have persistent borrelia infection. Patients with the genetic haplotype HLA-DR4 or DR2 seem to be at highest risk of chronic arthritis and this appears to have an immunologic basis.[25] Although it is possible that these HLA types inhibit the body's ability to fight the spirochete, a more likely explanation is that the initial Lyme infection initiates a chronic immune arthritis. Some of these patients benefit from intraarticular corticosteroids or synovectomy.[6]

Neurologic Disease

For minor neurologic, involvement (Bell's palsy) doxycycline, 100 to 200 mg twice daily for one month, may be considered appropriate therapy. In fact excellent results have been noted in nine patients on this regimen who had neurologic disease of short duration.[26] Of interest was that despite clinical success, cerebrospinal fluid (CSF) levels of doxycycline were often subtherapeutic.[26,27]

High-dose intravenous penicillin has also been effective in acute neurologic disease. In a small study Steere et al found that nine of 12 patients responded to 20 million units of penicillin given daily for 10 days.[28] In 1988 Pal et al reported a case of severe neurologic Lyme disease that was unresponsive to penicillin therapy but promptly responded to a combination of cefotaxime and corticosteroids.[29] In a small study of 21 patients there was no clinical difference in the outcome of patients with acute neurologic disease randomly treated with penicillin or cefotaxime.[30] Two of 10 patients in the penicillin group and two of the 11 patients in the cefotaxime group had persistent symptoms. Interestingly, penicillin was effective in this study despite the absence of bactericidal activity in the CSF.[30]

A more comprehensive study of a large number of patients by Hassler et al[24] demonstrated significantly better results with cefotaxime, 3 g every 12 hours, compared to Steere's regimen of high-dose penicillin. In patients with peripheral neuropathy there was resolution

Table 1

Suggested Treatment of Lyme Disease

Clinical Manifestation	*Preferred Therapy*	*Alternative Therapy*
1. Early Disease (eg, ECM)	Adult: Doxycycline 100 mg orally twice daily for 21 days	Amoxicillin 500 mg orally with or without probenacid 500 mg orally four times daily for 21 days
	Children (<8 years): Amoxicillin 250-500 mg orally four times daily for 21 days	Erythromycin 250 mg orally four times daily for 21 days
2. Arthritis, mild early neurologic disease (eg, Bell's palsy); mild cardiac disease (eg, first-degree heart block).	Adult: Doxycycline 100 mg twice daily for 30 days	Amoxicillin 500 mg and probenecid 500 mg orally four times daily for 30 days
	Children: Amoxicillin 250-500 mg orally four times daily for 30 days	Erythromycin 250 mg orally our times daily for 30 days
3. Arthritis or late neurologic disease unresponsive to oral therapy; acute severe neurologic disease; severe cardiac conduction disturbance (eg, high-degree heart block)	Adult: Ceftriaxone 2 g IV daily or cefotaxime 2 g IV every eight hours for two weeks	
	Children: Ceftriaxone or cefotaxime 100 mg per kg daily	

in 90% (26/29) of the cefotaxime treated patients and only 67% (20/30) of the penicillin group.

Ceftriaxone has also been extensively studied in the treatment of late neurologic disease. In a small study Dattwyler and colleagues found it to be superior to penicillin in the treatment of patients with fatigue or encephalopathies secondary to Lyme disease.[23] Although they initially employed 4 g of ceftriaxone daily, this dosage resulted in diarrhea in approximately 50% of patients A dosage reduction to 2 g daily was found to be as effective and the incidence of diarrhea fell to 10%.[23] Logigian et al[31] recently reported a response rate of 66% using two weeks of ceftriaxone therapy (2 g/day) in the treatment of late Lyme neurologic disease. These patients all had typical clinical and serologic findings for late Lyme disease.

To date, in only one study has ceftriaxone been compared with cefotaxime treatment in the neurologic manifestation of Lyme disease. Pfister et al[32] compared ceftriaxone 2 g daily to cefotaxime 2 g three times daily in patients with neurologic Lyme disease. Antibiotic concentrations in CSF were higher in the ceftriaxone group, but all but one patient in the cefotaxime group did have CSF levels above the MIC90 for *Borrelia burgdorferi*. At follow-up there was no significant difference between the two groups. Four of 12 of the ceftriaxone patients and six of 15 of the cefotaxime patients continued to have neurologic problems. One important finding is that *B. burgdorferi* was isolated from the CSF of a ceftriaxone patient 7 1/2 months after therapy. Because failure in the treatment of neurologic disease appears to imply persistence of infection, future studies employing 14 to 21 days of therapy appear indicated.

It can be seen from review of all studies that the success rate in treatment of long-standing neurologic disease is much less than in the treatment of acute disease.

General Rules of Therapy

It is apparent from the above discussion that the recommended therapy for each stage of Lyme disease continues to evolve and remains controversial. Our current treatment recommendations are outlined in Table 1. At present three principles should be followed: except in cases of significant neurologic or cardiac disease, the first attempt at treatment should be with oral antibiotic therapy; when treating a chronic disease the success or failure of treatment should not be judged at the time of therapy, but rather over a period of three to six months after the end of therapy; finally, parenteral therapy of patients with poorly documented diagnosis should be avoided.

REFERENCES

1. Steere AC, Malawista SE, Snydman DR, Shope RE, Andiman WA, Ross WR, Steele FM: Lyme arthritis. *Arthritis Rheum* 1977;20:7-17.
2. Ciesielski CA, Malakowitz LE, Horsley R, Hightower AW, Russell H, Broome CV: The geographic distribution of Lyme disease in the United States. *Ann NY Acad Scie* 1988;593:283-8.
3. Burgdorfer W, Barbour AG, Hayes SF, Benach JL, Grunwaldt E,

Davis JP: Lyme disease — A tick borne spirochetosis? *Science* 1982;216:1317-9.

4. Lyme disease—United States, 1987-1988. *MMWR* 1989;38:668-73.
5. Piesman J, Mather TN, Sinsky RJ, Spielman A: Duration of tick attachment and *Borrelia burgdorferi* transmission. *J Clin Microbiol* 1987;25:557-8.
6. Steere AC: Lyme disease. *New Engl J Med* 1989;321:586-96.
7. Reik L, Steere AC, Bartenhagen NH, Shope RE, Malawista SE: Neurologic abnormalities of Lyme disease. *Medicine* 1979;58:281-94.
8. Finkel MF: Lyme disease and its neurologic complications. *Arch Neurol* 1988;45:99-104.
9. Schwartz BS, Goldstein MD, Robeiro JM, Schulze TL: Antibody testing in Lyme disease. *JAMA* 1989;262:3431-4.
10. 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.
11. Duffy J, Mertz LE, Wobig GH, Katzman JA: Diagnostic Lyme disease: The contribution of serologic testing. *Mayo Clin Proc* 1988;63:1116-21.
12. Sigal LH: Summary of the first 100 patients seen at a Lyme disease referral center. *Am J Med* 1990;88: 577-81.
13. Kaell AT, Volkman DJ, Gorevic PD, Dattwyler RJ: Positive Lyme serology in subacute bacterial endocarditis. *JAMA* 1990;264 (22):2916-8.
14. Johnson RC, Kodner C, Russel M: In vitro and in vivo susceptibility of the Lyme disease spirochete *Borrelia burgdorferi*, to four antimicrobial agents. *Antimicrob Aqents Chemother* 1987;31:164-7.
15. Johnson, RC, Kodner C, Russel M, Girard D: In vitro and in vivo susceptibility of *Borrelia burgdorferi* to azithromycin. *J Antimicrob Chemother* 1990;25:33-8.
16. Steere AC, Malawista SE, Newman JH, Spieler PN, Bartenhagen NH: Antibiotic therapy in Lyme disease. *Ann Intern Med* 1980;93:1-8.
17. Dattwyler RJ, Halperin JJ: Failure of tetracycline therapy in early Lyme disease. *Arthritis Rheum* 1987;30:448-50.
18. Dattwyler RJ, Volkman DJ, Conaty SM: Amoxycillin plus probenecid versus doxycycline for treatment of erythema migrans borreliosis. *Lancet* 1990;336:1404-6.
19. Costello CM, Steere AC, Pinkerton RE, Feder HM Jr: Prospective study of tick bites in an endemic area for Lyme disease. *J Infect Dis* 1989;159:136-9.
20. Steere AC, Green J, Schoen RT, Taylor E, Hutchinson GJ, Rahn DW, Lamawista SE: Successful parenteral penicillin therapy of established Lyme arthritis. *N Engl J Med* 1985;312:869-74.
21. Liu NY, Dinerman H, Levin RE, et al: Randomized trial of doxycycline vs amoxicillin/probenecid for the treatment of Lyme arthritis; treatment of nonresponders with IV penicillin or ceftriaxone. *Arthritis Rheum* 1989;32:S46 abstract.
22. Dattwyler RJ, Halperin JJ, Pass H, Left BJ: Ceftriaxone as effective therapy in Lyme disease. *J Infect Dis* 1987;155:1322-5.
23. Dattwyler RJ, Halperin JJ, Volkman DJ, Left BJ: Treatment of late Lyme borreliosis-randomized comparison of ceftriaxone and penicillin. *Lancet* 1988;1:1191-4.
24. Hassler D, Zoller L, Haude M, Hufnagel HD, Heinrich F, Sonntage HG: Cefotaxime versus penicillin in the late stage of Lyme disease — Prospective, randomized therapeutic study. *Infection* 1980;18:16-20.
25. Steere AC, Dwyer E, Winchester R: Association of chronic Lyme arthritis with HLA-DR4 and HLA-DR2 alleles. *N Enql J Med* 1990;323:219-23.
26. Dotevall L, Alestig K, Hanner P, Norkrans G, Hagberg L: The use of doxycycline in nervous system Borrelia burgorferi infection. *Scand J Infect Dis* xxxx; 53 (suppl):74-9.
27. Dotevall L, Hagberg L: Penetration of doxycycline into cerebrospinal fluid in patients treated with suspected Lyme neuroborreliosis. *Antimicr Agents Chemother* 1989;33:1078-80.
28. Steere AC, Pachner AR, Malawista SE: Neurologic abnormalities of Lyme disease: Successful treatment with high-dose intravenous penicillin. *Ann Intern Med* 1989;99:767-72.
29. Pal GS, Baker JT, Wright DJM: Penicillin-resistant borrelia encephalitis responding to cefotaxime. *Lancet* 1988;1:50-1.
30. Pfister HW, Preac-Mursic V, Wilske B, Einhaupl KM: Cefotaxime vs penicillin G for accute neurologic manifestations in Lyme borreliosis. *Arch Neurol* 1989;46:1190-4.
31. Logigian EL, Kaplan RF, Steere AC: Chronic neurologic manifestations of Lyme disease. *N Engl J Med* 1990;323:1438-44.
32. Pfister HW, Mursic VP, Wilske B, Schielke E, Sorgel F: Randomized comparision of ceftriaxone and cefotaxime in Lyme neuroborreliosis. *J Infect Dis* 1991;163:311-8.