1997

Conn's Current Therapy

LATEST APPROVED METHODS OF TREATMENT
FOR THE PRACTICING PHYSICIAN

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phylaxis probably can be discontinued safely at age 21 years if at least 5 years have elapsed since the last attack of ARF.

In addition to rheumatic fever prophylaxis, patients with RHD require infective endocarditis prophylaxis on an episodic basis related to dental or surgical procedures or gastrointestinal or genitourinary tract instrumentation, as recommended by the American Heart Association.

LYME DISEASE

method of
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Lyme disease is an extremely complex illness that is still poorly understood. To date, there still is no consensus on many aspects of its management. Despite this, the diagnosis and treatment of Lyme disease is entering a new era, replacing simplistic approaches with more modern ones based on better knowledge, more experience, and the application of common sense. This has resulted in an expansion of syndromes attributable to Lyme disease, thus improving diagnosis, and new treatment recommendations regarding both drug and dose. The existence of seronegativity and chronic persistent infection have been confirmed, as have relapses and treatment failures. With more careful dosing and more prolonged treatment duration, chronic symptoms can be prevented or eliminated in many more patients than ever before.

The diagnosis of Lyme disease is made on clinical grounds, as no currently available test, no matter the source or type, is definitive in confirming whether an infection with *Borrelia burgdorferi* is present, or if so, whether the infection is responsible for the patient's symptoms.

Treatment is also difficult. It is impossible to know how much medication will be necessary to control the infection, because response to therapy is extremely variable. Also, it cannot be determined in advance which of the many complaints will improve with further antibiotics, and which will be permanent. There is no test available that can be used during therapy to indicate how effective the treatment regimen is, and there is no test for cure. That is why the entire clinical picture must be taken into account, including a search for the many subtleties that exist. Patient diaries that succinctly outline symptoms over a course of therapy are vital, and as many objective measures as possible should be followed, such as temperature graphs, notes from physical therapists, and physical findings. This information will help in your assessment of effectiveness of ongoing treatment and guide you in determining optimal duration.

The concept of a "therapeutic alliance" between the caregiver and patient has to be emphasized. This means that the patient has to become part of the medical team and take responsibility for complying with the recommendations given, maintaining the best possible health status, reporting promptly any problems or new symptoms, and especially in realizing that despite all our best efforts, success in diagnosis and treatment is never assured.

GENERAL INFORMATION

Lyme disease is an infectious illness caused by the spirochete *Borrelia burgdorferi* (Bb). Bb is transmitted by the bite of an ixodid tick. Transmission of the organism occurs if the tick has been attached long enough to become engorged (typically more than 24 hours), unless it has been removed improperly, in which case transmission can occur more rapidly. Squeezing the tick's body, irritating it with heat or chemicals in an attempt to get it to back out, and disrupting the tick's integrity, allowing its contents to spill into the wound, all are examples of this. This history is important to elicit when deciding whether to give antibiotic prophylaxis after a tick bite.

DIAGNOSIS

Because of the unreliability of serologic testing for Lyme disease, the diagnosis is a clinical one, based upon the type and pattern of symptoms present and their evolution over time, especially in the setting of a previously healthy patient who has had potential tick exposure. Erythema migrans is the sole absolute indicator of Lyme disease, yet it is observed in fewer than 50% of cases. The other and more common symptoms are nonspecific and protean, but they almost always involve multiple systems and vary over time in both location and intensity, consistent with an active, disseminated infection. A great deal of effort must be made in ruling out similarly presenting illnesses, for often disseminated Lyme becomes a diagnosis of exclusion. Another very important factor is response to treatment: presence or absence of Jarisch-Herxheimer–like reactions, and improvement with therapy. To simplify and clarify diagnosis, a workshop was convened in 1990 and a diagnostic scheme was developed (Table 1). It is important to note that the published reporting criteria of the Centers for Disease Control are for surveillance, not for diagnosis.

Erythema Migrans

Erythema migrans (EM) is a raised, warm, erythematous, centrifugally expanding round or oval lesion with distinct margins. Although usually painless, mild stinging or pruritus can occur. The EM rash can begin 4 days to several weeks after the bite, lasts for several weeks, and may or may not be associated with constitutional symptoms. Multiple lesions are present in 10% to 20% of pa-

TABLE 1. **Lyme Disease Diagnostic Criteria**

	Relative Value
Tick exposure in an endemic region	1
Systemic signs and symptoms consistent with Lyme (other potential diagnoses excluded):	
Single system, e.g., monoarthritis	1
Two or more systems, e.g., monoarthritis and facial palsy	2
Erythema migrans	7
Acrodermatitis chronica atrophicans, biopsy-confirmed	7
Seropositivity	2
Seroconversion on paired sera	3
Tissue microscopy, silver stain	3
Tissue microscopy, monoclonal immunofluorescence	4
Culture positivity	5
B. burgdorferi antigen recovery (when validated)	4
B. burgdorferi DNA/RNA recovery (when validated)	4
Diagnosis	
Lyme borreliosis likely	7 or above
Lyme borreliosis probable	5–6
Lyme borreliosis unlikely	4 or below

tients. A necrotic center may represent a mixed infection, involving other organisms besides *B. burgdorferi*. Atypical lesions may have to be biopsied to aid in diagnosis.

Serologic Testing

Because Lyme serologies often given inconsistent results, you may have to test at more than one laboratory, using different methods if possible. Western blotting is recommended for confirmation. IgM and IgG titers are often reported separately. In Lyme disease, elevated IgM levels do not always indicate an early stage, for these levels may repeatedly peak throughout the course of an active infection. False-negative serologies are common (estimated at 30%) and false-positives occur in up to 10% of patients. Approximately one-third of seronegative patients will become transiently seropositive after completion of successful treatment.

Considerable evidence suggests that in all disseminated Lyme infections, seeding of the central nervous system occurs early (possibly within hours after the bite), yet a recent study has shown that antibodies to Bb can be detected in the cerebrospinal fluid (CSF) in only 20% of such patients. Therefore, spinal taps are not routinely recommended but are performed in patients with pronounced neurologic manifestations, especially if they are seronegative or still significantly symptomatic after completion of treatment. They are done to rule out other neurologic conditions, to determine whether Bb antigens are present, and to determine whether Bb antibodies are being locally produced in the central nervous system. It is especially important to look for pleocytosis and elevated protein, which correlate with the need for more aggressive therapy, as well as the opening pressure, which can be elevated and add to headaches, especially in children.

TREATMENT GUIDELINES

Antibiotic Choices

Because the Lyme spirochete is rapidly distributed to all parts of the body, including the central nervous system, shortly after *B. burgdorferi* enters the bloodstream, all stages of this illness represent disseminated disease. The antibiotic and dose chosen must be able to penetrate all tissues in adequate concentrations to be bactericidal to the organism, even in early infections.

There is no universally effective antibiotic for treating Lyme disease. The antibiotic chosen and dose used will vary based on age, weight, gastrointestinal function, blood levels achieved in light of these factors, and on patient tolerance. For poorly understood reasons, serum antibiotic concentrations vary widely in Lyme patients. Therefore, whenever possible, serum antibiotic levels should be determined to aid in arriving at therapeutic doses.

Four types of antibiotics are in general use for Lyme treatment. The tetracyclines, including doxycycline and minocycline, are bacteriostatic at doses commonly prescribed, and unless high blood levels are attained, treatment failures in early and late disease are common. Tetracycline itself does not penetrate into the CSF as well as doxycycline and minocycline, and its use is not advised. Doxycycline can be very effective but only if adequate blood levels are achieved either by high oral doses (300 to 600 mg daily) or by parenteral administration.

Penicillins are bactericidal. As would be expected in managing an infection with a gram-negative organism such as *B. burgdorferi*, amoxicillin has been shown to be more effective than oral penicillin V. Because of its short half-life and need for high levels, amoxicillin is usually administered along with probenecid.

Cephalosporins are useful but must be of advanced generation: first-generation drugs are not effective, and second-generation drugs are comparable to amoxicillin and doxycycline both in vitro and in vivo. Third-generation agents are currently the most effective of the cephalosporins because of their very low mean bactericidal concentrations (MBCs) (0.06 for ceftriaxone) and because of excellent tissue penetration. Also, cephalosporins have been shown to be effective in penicillin and tetracycline failures. Cefuroxime axetil (Ceftin), a second-generation agent, is also effective against *Staphylococcus* and thus is useful in treating atypical erythema migrans that may represent a mixed infection, containing some of the more common skin pathogens in addition to Bb. Because it is difficult to tolerate due to gastrointestinal (GI) side effects and is costly, cefuroxime axetil is not used as a first-line drug.

Erythromycin has been shown to be almost ineffective. The advanced macrolides (they are classified as azalides) such as azithromycin (Zithromax) and clarithromycin (Biaxin) have impressively low MBCs, but can be difficult to tolerate due to poor GI tolerance at the high doses needed, and their excessive tendency to promote yeast overgrowth.

When choosing a third-generation cephalosporin, there are several points to remember: cefotaxime (Claforan) and ceftriaxone (Rocephin) both have demonstrated activity in vitro, in vivo, and in clinical studies. Ceftriaxone is administered once daily (an advantage for home therapy) but has 95% biliary excretion and can crystallize in the biliary tree with resultant colic and possible cholecystitis. Gastrointestinal excretion results in a large impact on gut flora. Cefotaxime, which must be given at least every 12, and preferably every 8 hours, is less convenient, but as it has only 5% biliary excretion, it never causes biliary concretions, and may have less impact on gut flora. Biliary complications and gastrointestinal superinfections with ceftriaxone can be lessened if this drug is given in interrupted courses, such as 5 days in a row each week. Table 2 contains a summary of antibiotic choices; other agents with demonstrated in vitro efficacy have been used successfully in treating Lyme patients and are also listed.

Treatment Categories

I have found conclusively that the duration of treatment is just as important as the choice of antibiotic. It is known that *B. burgdorferi* has a very long generation time and may have periods of dormancy.

TABLE 2. **Antibiotic Choices**

Oral Therapy

(Always check blood levels; goal is peak in midteens; trough [pre-dose] blood level should be greater than 3 μg/mL)

Amoxicillin:
- Adults: 1 gm q 8 h plus probenecid, 500 mg q 8 h
- Pregnancy: 1 gm q 6 h
- Children: 50 mg/kg/day divided into q 8 h doses

Doxycycline:
- Adults: 100 mg tid with food
- Not for children or in pregnancy

Cefuroxime axetil (Ceftin): oral alternative that may be effective in amoxicillin and doxycycline failures; useful in erythema migrans rashes co-infected with common skin pathogens
- Adults and pregnancy: 1 gm q 12 h
- Children: 125 to 500 mg q 12 h based on weight

Tetracycline: Poor response and not recommended

Erythromycin: Poor response and not recommended

Chloramphenicol: Not recommended as not proved and potentially toxic

Poorly Studied but Anecdotally Effective Alternatives

Azithromycin (Zithromax):
- Adults: 500 to 1000 mg/d
- Adolescents: 250 to 500 mg/d
- Cannot be used in pregnancy or in younger children

Clarithromycin (Biaxin):
- Adults: 250 to 500 mg q 6 h
- Cannot be used in pregnancy or in younger children

Parenteral Therapy

Ceftriaxone (Rocephin): Risk of biliary sludging can be minimized with intermittent breaks in therapy (i.e., infuse 5 d in a row per wk)
- Adults and pregnancy: 2 gm q 24 h
- Children: 75 mg/kg/d up to 2 gm/d

Cefotaxime (Claforan): Comparable efficacy to ceftriaxone; no biliary complications
- Adults and pregnancy: 2 gm q 8 h
- Children: 90 to 180 mg/kg/d dosed q 6 h

Doxycycline: Requires central line as it is caustic
- Adults: 300 mg q 24 h, then adjust based upon blood levels
- Cannot be used in pregnancy or in younger children

Penicillin G: IV penicillin G is minimally effective and not recommended

Benzathine penicillin: Useful alternative to oral therapy
- Adults: 1.2 million U once to twice weekly, based upon body weight
- Adolescents: 300,000 to 1.2 million U weekly
- Cannot be used in pregnancy

Poorly Studied but Anecdotally Effective Alternatives

Imipenem: Similar in efficacy to cefotaxime. Must be given q 6 to 8 h

Cefuroxime: Not demonstrably better than ceftriaxone or cefotaxime

Ampicillin: More effective than penicillin G. Must be given q 6 h

This has a major effect on the length of treatment needed for the various stages of this illness, for the longer one is infected before adequate treatment is begun, the longer the treatment course will have to be. In humans, Bb seems to regenerate monthly. As antibiotics kill organisms only during their growth phase, therapy is designed to bracket at least one entire 4-week generation cycle. Hence the minimum treatment course is 6 weeks; late, disseminated infections may have to be treated for many months to be controlled. During treatment, symptoms will wax and wane every 4 weeks, reflecting the growth period of this *Borrelia*, similar to what is seen in the relapsing fevers. If the antibiotics are working, over time these monthly flares will lessen in severity and duration. To prevent relapses, treatment has to be continued until all signs of active infection have cleared. The average duration of successful therapy of advanced cases is 4 months in males, and 6 months in hormonally active females. Treatment failures should alert the clinician to alternative diagnoses, concurrent conditions, and the presence of an otherwise inapparent immune deficiency.

With intravenous antibiotic therapy, a 6-week course is the minimum. If there is a pronounced flare of symptoms during the fourth week, then extend the course to 10 weeks to bracket the next generation cycle. This type of clinical assessment continues, and when these monthly reactions finally lessen in severity, then oral medications can be substituted to the same end point as mentioned earlier. The very occurrence of ongoing monthly cycles indicates that living organisms are still present and that antibiotic should be continued until these cycles no longer occur. Treatment categories are presented in Table 3.

There is more to managing Lyme disease tha

TABLE 3. **Treatment Categories**

Prophylaxis of high-risk groups should consist of education and preventive measures; antibiotics not recommended

Embedded Deer Tick with No Signs or Symptoms of Lyme:

Decide to treat based on the type of tick, whether it came from an endemic area and percent infected, how it was removed, and length of attachment (nymphs: at least 1 day; adults: anecdotally, as little as 4 hours). The risk of transmission is greater if the tick is engorged, or if it was removed improperly, allowing the tick's contents to spill into the bite wound. High-risk bites are treated as follows:

Adults: Oral therapy for 14 days
Pregnancy: Amoxicillin, 1000 mg q 6 h for 6 wk
  Alternative: Cefuroxime axetil, 1000 mg q 12 h for 6 wk
Young children: Oral therapy for 14 days
  Erythromycin: Poor alternative with documented treatment failures

Early Localized: Single erythema migrans with no constitutional symptoms:

Adults and children: Oral therapy for 6 weeks
Pregnancy: 1st and 2nd trimesters: IV for 21 days, then oral for 6 weeks;
  3rd trimester: amoxicillin 1000 mg q 6 h for 6 weeks

Disseminated Disease: Multiple lesions, constitutional symptoms, lymphadenopathy, or any other manifestations of late disease:

Early Disseminated: Present for less than 1 year and not complicated by immune deficiency or prior steroid treatment:

Adults: Oral therapy until no active disease for 4 weeks (4–6 months total)
Pregnancy: As in localized disease, but duration as above. Some experienced clinicians treat throughout pregnancy.
Children: Oral therapy with duration based upon clinical response

Parenteral Alternatives: For sicker patients and those unresponsive to or intolerant of oral medications:

Adults and children: IV therapy for 6 weeks or until clearly improved; follow with oral therapy or IM benzathine penicillin until no active disease for 4 weeks
Pregnancy: IV then oral therapy as above

Late Disseminated: Present greater than 1 year, more severely ill patients, and those with prior significant steroid therapy or any other cause of impaired immunity:

Adults and pregnancy: extended IV therapy (6 to 10 or more weeks), then oral or IM to same end point.
Children: IV therapy for 6 or more weeks

simply prescribing antibiotics. It is necessary for the patient to obtain adequate rest and receive any needed physical therapy. Those who have been ill for a prolonged period will also benefit immensely from a careful, thorough, and aggressive graded exercise program when they are well enough to begin. Thrush has to be controlled, and a sensible regimen of adequate nutrition and vitamins, abstinence from smoking and alcohol, and avoidance of caffeine is recommended. Supportive measures cannot be ignored. Table 4 summarizes these points.

Unfortunately, not every Lyme patient will regain his or her former health, and the management of refractory disease is presented in Table 5.

TABLE 4. **Adjunctive Therapy**

Recommended in All Lyme Patients:

Daily yogurt or acidophilus preparations
Multivitamins and B complex, 50 mg daily
Physical therapy and rehabilitation

Prescribe as Needed, Especially in More Severe Cases:

Analgesics and muscle relaxants
NSAIDs and remittive agents
Immune globulins and other immunotherapy if indicated
Antidepressants
Psychosocial evaluation and possibly refer for counseling

Contraindicated:

Alcohol use
Excessive caffeine intake
Any avoidable stresses
Significant sleep deprivation

The ever growing number of new cases of this illness underscores the need for better preventive measures, and the many chronically afflicted patients who are resistant to treatment indicate that more research is needed in this area.

TABLE 5. **Refractory Disease**

Persistent Signs and Symptoms That Respond to Antibiotic Therapy

Patients in this group improve on antibiotics, yet relapse repeatedly when medications are discontinued. Persistent infection, somehow resistant to treatment, has been demonstrated in some patients in this category. Recommended: study immune competence, search for concurrent infections, and reconsider the diagnosis

Options for Treatment

Longer duration, including open-ended maintenance therapy
Increased dose
Different drug
Change method of administration (oral to IV)
Supportive therapy as needed

Persistent Signs and Symptoms Not Responsive to Antibiotics

Reconsider the diagnosis
Supportive therapy based on symptoms
NSAIDs and hydroxychloroquine
Antidepressants, analgesics, and muscle relaxants
Synovectomy if the nonjoint symptoms are minimal
Psychiatric/psychometric evaluation
Long-term follow-up
Consider retreatment if condition changes