



ASHEVILLE INTEGRATIVE MEDICINE

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Lyme Disease

MAJOR RECOMMENDATIONS - Highlights of Guidelines

- Since there is currently no definitive test for Lyme disease, laboratory results should not be used to exclude an individual from treatment.
- Lyme disease is a clinical diagnosis and tests should be used to support rather than supersede the physician's judgment.
- The early use of antibiotics can prevent persistent, recurrent, and refractory Lyme disease.
- The duration of therapy should be guided by clinical response, rather than by an arbitrary (i.e., 30 day) treatment course.
- The practice of stopping antibiotics to allow for delayed recovery is not recommended for persistent Lyme disease. In these cases, it is reasonable to continue treatment for several months after clinical and laboratory abnormalities have begun to resolve and symptoms have disappeared.

Diagnostic Concerns - The most important method for preventing chronic Lyme disease is recognition of the early manifestations of the disease.

Atypical Early Presentations

Early Lyme disease classically presents with a single erythema migrans (EM or "bull's-eye") rash. The EM rash may be absent in over 50% of Lyme disease cases, however. Patients should be made aware of the significance of a range of rashes beyond the classic EM, including multiple, flat, raised, or blistering rashes. Central clearing was absent in over half of a series of EM rashes. Rashes can also mimic other common presentations including a spider bite, ringworm, or cellulitis.

Physicians should be aware that fewer than 50% of all Lyme disease patients recall a tick bite. Early Lyme disease should also be considered in an evaluation of "off-season" onset when flu-like symptoms, fever, and chills occur in the summer and fall. Early recognition of atypical early Lyme disease presentation is most likely to occur when the patient has been educated on this topic.

New Chronic Lyme Disease Presentations

A detailed history may be helpful for suggesting a diagnosis of chronic Lyme disease. Headache, stiff neck, sleep disturbance, and problems with memory and concentration are findings frequently associated with neurologic Lyme disease. Other clues to Lyme disease have been identified, although these have not been consistently present in each patient: numbness and tingling, muscle twitching, photosensitivity, hyperacusis, tinnitus, lightheadedness, and depression.

Most patients diagnosed with chronic Lyme disease have an indolent onset and variable course. Neurologic and rheumatologic symptoms are characteristic, and increased severity of symptoms on waking is common. Neuropsychiatric symptoms alone are more often seen in chronic than acute Lyme disease. Although many studies have found that such clinical features are often not unique to Lyme disease, the striking association of musculoskeletal and neuropsychiatric

symptoms, the variability of these symptoms, and their recurrent nature may support a diagnosis of the disease.

The Limitations of Physical Findings

A comprehensive physical examination should be performed, with special attention to neurologic, rheumatologic, and cardiac symptoms associated with Lyme disease.

Physical findings are nonspecific and often normal, but arthritis, meningitis, and Bell's palsy may sometimes be noted. Available data suggest that objective evidence alone is inadequate to make treatment decisions, because a significant number of chronic Lyme disease cases may occur in symptomatic patients without objective features on examination or confirmatory laboratory testing.

Factors other than physical findings, such as a history of potential exposure, known tick bites, rashes, or symptoms consistent with the typical multisystem presentation of Lyme disease, must also be considered in determining whether an individual patient is a candidate for antibiotic therapy.

Sensitivity Limitations of Testing

Treatment decisions should not be based routinely or exclusively on laboratory findings. The two-tier diagnostic criteria, requiring both a positive enzyme-linked immunosorbent assay (ELISA) and western blot, lacks sensitivity and leaves a significant number of individuals with Lyme disease undiagnosed and untreated. These diagnostic criteria were intended to improve the specificity of tests to aid in identifying well-defined Lyme disease cases for research studies. Though arbitrarily chosen, these criteria have been used as rigid diagnostic benchmarks that have prevented individuals with Lyme disease from obtaining treatment. Diagnosis of Lyme disease by two-tier confirmation fails to detect up to 90% of cases and does not distinguish between acute, chronic, or resolved infection.

The Centers for Disease Control and Prevention (CDC) considers a western blot positive if at least 5 of 10 immunoglobulin G (IgG) bands or 2 of 3 immunoglobulin M (IgM) bands are positive. However, other definitions for western blot confirmation have been proposed to improve the test sensitivity. In fact, several studies showed that sensitivity and specificity for both the IgM and IgG western blot range from 92 to 96% when only two specific bands are positive.

Lumbar puncture has also been disappointing as a diagnostic test to rule out concomitant central nervous system infection. In Lyme disease, evaluation of cerebrospinal fluid is unreliable for a diagnosis of encephalopathy and neuropathy because of poor sensitivity. For example, pleocytosis was present in only one of 27 patients (sensitivity 3%) and with only seven cells. The antibody index was positive (>1) in only one of 27 patients (sensitivity 3%). An index is the ratio between Lyme ELISA antibodies in the spinal fluid and Lyme ELISA antibodies in the serum. The proposed index of 1.3 would be expected to have even worse sensitivity.

Several additional tests for Lyme disease have been evaluated. These include antigen capture, urine antigen, and polymerase chain reaction. Each has advantages and disadvantages in terms of convenience, cost, assay standardization, availability, and reliability. These tests remain an option to identify people at high risk for persistent, recurrent, and refractory Lyme disease but have not been standardized.

Seronegative Lyme Disease

A patient who has tested seronegative may have a clinical presentation consistent with Lyme disease, especially if there is no evidence to indicate another illness. Although many individuals do not have confirmatory serologic tests, surveillance studies show that these patients may have a similar risk of developing persistent, recurrent, and refractory Lyme disease compared with the seropositive population.

Continued Importance of Differential Diagnosis

The differential diagnosis of Lyme disease requires consideration of both infectious and noninfectious etiologies. Among noninfectious causes are thyroid disease, degenerative arthritis, metabolic disorders (vitamin B12 deficiency, diabetes), heavy metal toxicity, vasculitis, and primary psychiatric disorders.

Infectious causes can mimic certain aspects of the typical multisystem illness seen in chronic Lyme disease. These include viral syndromes, such as parvovirus B19 or West Nile virus infection, and bacterial mimics, such as relapsing fever, syphilis, leptospirosis, and mycoplasma.

The clinical features of chronic Lyme disease can be indistinguishable from fibromyalgia and chronic fatigue syndrome. These illnesses must be closely scrutinized for the possibility of etiological *Borrelia burgdorferi* infection.

Clinical Judgment

Clinical judgment remains necessary in the diagnosis of late Lyme disease. A problem in some studies that relied on objective evidence was that treatment occurred too late, leaving the patient at risk for persistent and refractory Lyme disease.

As noted, time-honored beliefs in objective findings and two-tier serologic testing have not withstood close scrutiny. Lyme disease should be suspected in patients with newly acquired or chronic symptoms (headaches, memory and concentration problems, and joint pain). Management of patients diagnosed on the basis of clinical judgment needs to be tested further in prospective trials, and diagnostic reproducibility must be verified.

Testing for Coinfection

Polymicrobial infection is a new concern for individuals with Lyme disease, and coinfection is increasingly reported in critically ill individuals. Although *B. burgdorferi* remains the most common pathogen in tick-borne illnesses, coinfections including *Ehrlichia* and *Babesia* strains are increasingly noted in patients with Lyme disease, particularly in those with chronic illness. *Bartonella* is another organism that is carried by the same ticks that are infected with *B. burgdorferi*, and evidence suggests that it is a potential coinfecting agent in Lyme disease.

Recent animal and human studies suggest that Lyme disease may be more severe and resistant to therapy in coinfecting patients. Thus, concurrent testing and treatment for coinfection is mandatory in Lyme disease patients.

Treatment Considerations: Since Lyme disease can become persistent, recurrent, and refractory even in the face of antibiotic therapy, evaluation and treatment must be prompt and aggressive.

Prompt Use of Antibiotics- Although no well designed studies have been carried out, the available data support the prompt use of antibiotics to prevent chronic Lyme disease. Antibiotic therapy may need to be initiated upon suspicion of the diagnosis, even without definitive proof. Neither the optimal antibiotic dose nor the duration of therapy has been standardized, but limited data suggest a benefit from increased dosages and longer treatment, comparable to the data on tuberculosis and leprosy which are caused by similarly slow-growing pathogens.

Choosing an Antibiotic - In acute Lyme disease, the choice of antibiotics should be tailored to the individual and take into account the severity of the disease as well as the patient's age, ability to tolerate side effects, clinical features, allergy profile, comorbidities, prior exposure, epidemiologic setting, and cost.

Conversely, persistent and refractory Lyme disease treatment is more likely to include intravenous and/or intramuscular antibiotics. The choices depend in part on the patient's response to antibiotic therapy and on the success of antibiotics in treating other Lyme disease patients.

Therapy usually starts with oral antibiotics, and some experts recommend high dosages. The choice of antibiotic therapy is guided by weighing the greater activity of intravenous antibiotics in the central nervous system against the lower cost and easy administration of oral antibiotics for *B. burgdorferi*.

Oral Antibiotic Options - For many Lyme disease patients, there is no clear advantage of parenteral therapy. Along with cost considerations and pressure to treat patients with Lyme disease with the least intervention, there is growing interest in the use of oral therapy.

First-line drug therapies for Lyme disease may include (in alphabetical order): oral amoxicillin, azithromycin, cefuroxime, clarithromycin, doxycycline, and tetracycline. These antibiotics have similar favorable results in comparative trials of early Lyme disease.

Intravenous Antibiotic Options - It is common practice to consider intravenous antibiotics upon failure of oral medications in patients with persistent, recurrent, or refractory Lyme disease, and as the first line of therapy for certain conditions, (i.e., encephalitis, meningitis, optic neuritis, joint effusions, and heart block).

Ideally, the intravenous antibiotic should be selected on the basis of in vitro sensitivity testing or clinical experience. Intravenous antibiotics are also justified by concern for penetration into the central nervous system.

Until recently, ceftriaxone, cefotaxime, and penicillin were the only intravenous antibiotics routinely studied for use in Lyme disease. Intravenous imipenem, azithromycin, and doxycycline have an adequate antispirochetal spectrum of activity and may represent suitable alternative therapies. However, the latter two drugs are often considered for intravenous use only if they are not tolerated orally.

Intramuscular Antibiotic Options - Intramuscular benzathine penicillin (1.2 to 2.4 million units per week) is sometimes effective in patients who do not respond to oral and intravenous antibiotics. If intramuscular benzathine penicillin is used, long-term therapy may be necessary due to the low serum concentration of this form of penicillin. Benzathine penicillin has mainly been used in patients who have had multiple relapses while receiving oral or intravenous antibiotic therapy or who are intolerant of oral or intravenous antibiotics.

Combination Antibiotic Treatment - Combination therapy with two or more antibiotics is now increasingly used for refractory Lyme disease and has also been given as initial therapy for some chronic presentations.

This approach is already used for another tick-borne illness, babesiosis. Oral amoxicillin, cefuroxime, or (more recently) cefdinir combined with a macrolide (azithromycin or clarithromycin) are examples of combination regimens that have proven successful in clinical practice, although controlled clinical trials are lacking in persistent, recurrent, and refractory Lyme disease.

Combination therapy in patients with Lyme disease raises the risk of adverse events. This risk must be weighed against the improved response to combination therapy in Lyme disease patients failing single agents.

Sequential Treatment - Clinicians increasingly use the sequence of an intravenous antibiotic followed by an oral or intramuscular antibiotic. In two recent case series that employed combination therapy and sequential therapy, most patients were successfully treated. A logical

and attractive sequence would be to use intravenous therapy first (e.g., intravenous ceftriaxone), at least until disease progression is arrested and then follow with oral therapy for persistent and recurrent Lyme disease.

Dosage - Increasingly, clinicians recommend that certain drugs used for Lyme disease be given at higher daily doses: for example, 3,000–6,000 mg of amoxicillin, 300–400 mg doxycycline, and 500–600 mg of azithromycin. Some clinicians prescribe antibiotics using blood levels to guide higher doses. Close monitoring of complete blood counts and chemistries are also required with this approach.

With higher doses, there may be an increase in adverse events in general and gastrointestinal problems in particular. *Acidophilus* has reportedly reduced the incidence of *Clostridium difficile* colitis and non-*C. difficile* antibiotic-related diarrhea.

Serious adverse effects of antibiotics, however, were less common than previous estimates. In a recent clinical trial of chronic Lyme disease, the overall serious adverse event rate was 3% after three months of antibiotics, including 1 month of intravenous antibiotics. Clinicians who have experience with higher dose antibiotic therapy must balance the benefit of higher drug levels achieved with this therapy against the modest risk of gastrointestinal and other side effects.

Duration of Therapy - Because of the disappointing long-term outcome with shorter courses of antibiotics, the practice of stopping antibiotics to allow for a delayed recovery is no longer recommended for patients with persistent, recurrent, and refractory Lyme disease. Reports show failure rates of 30–62% within 3 years of short-course treatment using antibiotics thought to be effective for Lyme disease. Conversely for neurologic complications of Lyme disease, doubling the length of intravenous ceftriaxone treatment from 2 to 4 weeks improved the success rate from 66 to 80%.

The management of chronic Lyme disease must be individualized, since patients will vary according to severity of presentation and response to previous treatment.

Concurrent risk factors (i.e., coinfections, previous treatment failures, frequent relapses, neurologic involvement, or previous use of corticosteroids) or evidence of unusually severe Lyme disease should lead to the initiation of prolonged and/or intravenous antibiotic treatment. Physicians should always assess the patient's response to treatment before deciding on appropriate duration of therapy (i.e., weeks versus months).

Empiric Treatment - The importance of establishing the diagnosis of Lyme disease is heightened in light of increasing concern about antibiotic overuse. After an appropriate history, physical examination, and laboratory testing are completed, empiric antimicrobial therapy should be initiated on the basis of clinical clues, the severity of the patient's acute illness, underlying disease, and the likelihood of *B. burgdorferi* infection. The International Lyme and Associated Diseases Society (ILADS) working group recommends that empiric treatment be considered routine for patients with a likely diagnosis of Lyme disease.

Persistent Lyme Disease - Persistent Lyme disease is more resistant to treatment and more likely to produce a relapse. Although persistent Lyme disease may resolve without additional therapy, many experts believe that this condition should be treated with repeated and prolonged antibiotics. Physicians should extend the duration of antibiotics to prevent or delay recurrent and refractory Lyme disease.

Recurrent Lyme Disease - Despite previous antibiotic treatment, Lyme disease has a propensity for relapse and requires careful follow-up for years. The data suggest that failure to eradicate the organism may be the reason for a recurrence of symptoms. Early and aggressive treatment

with antibiotics is indicated for recurrent Lyme disease. The ultimate impact from retreating each episode of recurrent Lyme disease is currently unclear.

Refractory Lyme Disease

Refractory Lyme disease is a devastating condition that usually affects patients with persistent symptomatology and long-term disability. Prompt and aggressive institution of antibiotic therapy may be essential to prevent refractory disease. Increasing evidence shows that antibiotics have a beneficial effect on the course of refractory Lyme disease even in cases where the patient is intolerant of antibiotics or when a previous regimen has failed. Several months of therapy are often required to produce clear evidence of improvement. During this time, symptomatic treatment may be combined with antibiotic treatment.

Treatment Failure - When patients fail to respond or their conditions deteriorate after initiation of empiric therapy, a number of possibilities should be considered other than Jarisch-Herxheimer reaction. These include adverse events that limit treatment, allergic history to medication, inappropriate or inadequate dosing regimen, compliance problems, incorrect medication, immune sequelae, and sequestering of the organism (e.g., in the central nervous system). An alternative diagnosis or coinfection should also be considered.

Symptomatic Treatment - Although there may be a potential role for symptomatic treatment in chronic Lyme disease, this approach has little support due to the strong possibility of persistent infection. Owing to the potential hazard of immunosuppression and the poor outcome in one study, steroid therapy is not recommended. Surgical synovectomy is associated with significant morbidity and does not address neurologic presentations; it should be reserved for knee pain failing antibiotic treatment. Intra-articular steroid injection may be useful as a temporizing procedure in patients with persistent knee pain but this runs the risk of masking persistent infection.

Symptomatic therapy (particularly anti-inflammatory medications, tricyclic antidepressants, selective serotonin re-uptake inhibitors, and hydroxychloroquine) may be useful in concert with antibiotics and in individuals failing antibiotics.

Hyperbaric oxygen therapy (HBOT) is under study but is not recommended for routine therapeutic use. Other treatments, including cholestyramine (CSM), antifungal therapy, and antiviral agents require further study.

Since patients are becoming more interested in alternative therapies (e.g., traditional Chinese medicine, anti-oxidants, hyperthermia, bee venom, naturopathy and homeopathy), physicians should be prepared to address questions regarding these topics.

Fibromyalgia - The outcome of treating fibromyalgia secondary to Lyme disease with nonantibiotic regimens has been poor. The most encouraging clinical trial showed success in only one of 15 patients and only modest improvement in 6 of 15 individuals with fibromyalgia despite 2 years of treatment.

Antibiotic therapy has been much more effective than supportive therapy in symptomatic patients with fibromyalgia secondary to Lyme disease.

Fibromyalgia treatment alone without antibiotics raises the risk of conversion to refractory chronic Lyme disease and/or exacerbation of an undiagnosed persistent infection and is not recommended. Increasingly, clinicians do not feel comfortable treating fibromyalgia in Lyme disease without antibiotics.

Decision to Stop Antibiotics

Several studies of patients with Lyme disease have recommended that antibiotics be discontinued after 30 days of treatment. Complicating the decision to stop antibiotics is the fact

that some patients present with disease recurrence after the resolution of their initial Lyme disease symptoms. This is consistent with incomplete antibiotic therapy. Although the optimal time to discontinue antibiotics is unknown, it appears to be dependent on the extent of symptomatology, the patient's previous response to antibiotics, and the overall response to therapy (see below).

Rather than an arbitrary 30-day treatment course, the patient's clinical response should guide duration of therapy. Patients must therefore be carefully evaluated for persistent infection before a decision is made to withhold therapy.

The decision to discontinue antibiotics should be made in consultation with the patient and should take into account such factors as the frequency and duration of persistent infection, frequency of recurrence, probability of refractory Lyme disease, gains with antibiotics, the importance to the patient of discontinuing antibiotics, and potential for careful follow-up.

The ideal approach would be to continue therapy for Lyme disease until the Lyme spirochete is eradicated. Unfortunately there is currently no test available to determine this point. Therefore, the clinician must rely on the factors outlined above to decide on the length of antibiotic therapy for chronic Lyme disease.

Alternative Antibiotics

There is compelling evidence that Lyme disease can result in serious and potentially refractory illness. Use of alternative antibiotics to treat early Lyme disease with erythema migrans is generally not indicated unless coinfection is suspected.

The ILADS Working Group believes that the risk of alternative antibiotics is acceptable in selected Lyme disease patients presenting with chronic Lyme disease. Alternative antibiotics include less commonly used oral antibiotics (cefixime, cefdinir, metronidazole) and intravenous antibiotics (imipenem, azithromycin). The role of alternative antibiotics in low-risk patients is less certain and there is less consensus among the guideline developers as to whether the potential benefits outweigh the risks.

Therapy for Coinfection

Therapy for polymicrobial infection in Lyme disease is a rapidly changing area of clinical practice. Uncomplicated Lyme disease may be managed without addressing coinfection by means of standard oral or parenteral antibiotic therapy. Some but not all experts recommend therapy for subclinical or chronic coinfection with *Ehrlichia*, *Babesia*, or *Bartonella* on the basis of their belief that responses are more prompt with this approach.

The dose, duration, and type of treatment for coinfections have not been defined. Published reports of coinfection are limited to a small number of patients treated in open-label, nonrandomized studies. Doxycycline has been indicated for *Ehrlichia*. A recently published randomized trial determined that treatment of severe *Babesia microti* with the combination of atovaquone and azithromycin was as effective as the use of standard oral therapy with clindamycin and quinine.

The decision to use alternative antibiotics should be based on the individual case, including a careful assessment of the patient's risk factors and personal preferences. Patients managed in this way must be carefully selected and considered reliable for follow-up. Further controlled studies are needed to address the optimal antimicrobial agents for coinfections and the optimal duration of therapy.