Lyme Disease: From Early Localized Disease to Post-Lyme Disease Syndrome
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ABSTRACT
Lyme disease cases have reached epidemic numbers in areas of the United States in recent years. Early diagnosis and treatment are essential to prevent serious complications. It is imperative that nurse practitioners be familiar with signs and symptoms of the disease, interpretation of test results, and recommended treatment options. They must also understand the current evidence-based practices related to post-Lyme disease syndrome in order to provide patients with accurate information and options. This article provides nurse practitioners with the necessary information to diagnose and treat patients with Lyme disease, from early infection to post-Lyme disease syndrome.

Keywords: Lyme disease, post-Lyme disease syndrome, tick-borne illness

O
er the past several decades, Lyme disease (LD) has become a serious public health concern in some areas of the United States and Europe. LD, first recognized in the 1970s when it was identified as the cause of a cluster of pediatric arthritis cases in Lyme, Connecticut, has quickly emerged as a growing epidemic. Since becoming a nationally notifiable disease in 1991, the number of cases has almost quadrupled from under 8,000 in 1991 to more than 30,000 in 2009. It is believed that the disease is widely underreported and the true incidence may reach the hundreds of thousands. There is no debate that LD is a growing epidemic. If left untreated, the illness can result in serious adverse sequelae affecting the skin, nervous system, joints, and heart. It is also known that some patients suffer prolonged neurocognitive and somatic symptoms after treatment for LD. In general, agreement exists concerning the presentation and treatment of early localized and disseminated disease. However, controversy abounds concerning the diagnosis of chronic LD. While a small minority of patients with a history of the disease continues to experience symptoms after treatment, the true cause of the often subjective complaints, as well as the appropriate treatment, remains unclear. This article provides an overview of the diagnosis and treatment of LD, along with a discussion of the science and controversy surrounding chronic LD and post-Lyme disease syndrome (PLDS).

DISEASE OVERVIEW & PRESENTATION
LD is the most common tick-borne illness in the US and Europe. It is the result of an infection with the spirochete *Borrelia burgdorferi*, which is transmitted by a bite from the tick species *Ixodes scapularis* and *Ixodes pacificus*. Animal studies have shown that there is a delay of 36 hours from the time the tick attaches to the host to transmission of the spirochete. Most infections occur between May and November, with a peak incidence in June and July. It is also important to note that only 25% to 30% of patients diagnosed with LD are able to recall a tick bite.

Patients with LD may present with an array of symptoms affecting various body systems, depending on the stage of the disease and length of time since infection. The stages of disease include early localized infection, early disseminated infection, and late LD. Early localized infection occurs first, with the development of erythema migrans, the most common clinical manifestation, occurring 7 to 14 days after tick detachment. Erythema migrans is characterized by a rapidly expanding erythematous lesion with central clearing (Figure 1). Approximately half of patients also develop flu-like symptoms at this stage of illness, including fever, headache, myalgias, stiff
neck, and fatigue, with a lack of gastrointestinal or respiratory symptoms.1,6

Early disseminated disease occurs weeks to months after the localized infection in 50% of untreated patients when the spirochete is spread through hematologic or lymphatic channels. Patients with disseminated disease may present with secondary annular lesions, generalized lymphadenopathy, and fatigue. Neurologic manifestations may include meningitis, Bell’s palsy, cranial neuritis, and radiculoneuritis. Cardiac manifestations most commonly include atrioventricular block, but myopericarditis or pancarditis may occur. Musculoskeletal symptoms such as migratory muscle and joint pain may be present.1,9

Late manifestations of LD, although uncommon, can occur months to years after initial infection in patients who were not treated or inadequately treated. Late LD is characterized by rheumatologic and neurologic symptoms, including arthritis, subacute encephalopathy,encephalomyelitis, and neuropathies.1

DIAGNOSIS

Because of the varied presentations of LD and the similarities to many other conditions, correct diagnosis can be difficult. When making a diagnosis and interpreting lab results, it is important for the nurse practitioner (NP) to understand the pretest probability of disease. Patients in endemic areas with objective signs of LD have a high pretest probability. A clinical diagnosis is appropriate in these patients and is the basis for most diagnoses of LD because of limitations in laboratory testing.9

The Centers for Disease Control and Prevention (CDC) recommend 2-tiered testing for an accurate diagnosis. This consists of completing an enzyme immunoassay (EIA) or immunofluorescence assay (IFA) first. If this test is positive or equivocal, an IgM and IgG Western Blot should be performed if the patient has had symptoms for less than 30 days. If the patient has had signs or symptoms for more than 30 days, only the IgG Western Blot is done.10 If the EIA or IFA are negative, the NP should consider other diagnoses or a convalescent serum in patients with symptoms for less than 30 days (Figure 2).10

There are several limitations to the laboratory testing for LD. IgM antibodies do not appear until 2-4 weeks after the onset of symptoms, and IgG antibodies do not appear for 4-6 weeks.9 Therefore, in some patients with early disease, the diagnosis must be made based on clinical findings. The IgM usually declines after 4-6 months of disease, while the IgG remains present even after treatment.9

When using 2-tiered testing, an important factor is the number of reactive bands: a positive serum will react with 5 to 10 scored bands on the IgG assay and 2 to 3 scored bands on the IgM assay. Uninfected patients will usually have at least 1 reactive band from a previous infection with a different organism.11 An incorrect interpretation of results may lead to an incorrect diagnosis of LD. Skipping steps in the 2-step process increases the false positive rate from 1.5% to 8%, depending on the population.11

Culturing B. burgdorferi is very difficult, making it challenging to discern whether viable organisms are present; therefore, antibody testing is preferred. There
are also many unvalidated testing methods for LD, which the CDC and Food and Drug Administration do not recommend. These include capture assays for antigens in urine, culture, immunofluorescence staining, cell sorting of cell wall-deficient or cystic forms, CD57 lymphocyte assays, measurement of antibodies in synovial fluid, or lymphocyte transformation tests.12

**TREATMENT**

According to guidelines from the Infectious Diseases Society of America (IDSA), which were published in 2006 and reviewed in 2010, antibiotics are recommended for all cases of LD, but length of treatment and route of administration differ, depending on stage of illness.5,13 Early localized or early disseminated disease without neurologic or cardiac manifestations should be treated with doxycycline 100 mg twice daily, amoxicillin 500 mg 3 times daily, or cefuroxime axetil 500 mg twice daily for 2 to 3 weeks. Macrolides have been found to be less effective and should not be used as first-line therapy, while first generation cephalosporins are ineffective and should not be used at all.5,13

Early disseminated disease with neurologic or cardiolologic manifestations should be treated with ceftriaxone 2 g per day intravenously for 10 to 28 days or doxycycline 200 to 400 mg twice daily for 10 to 28 days in patients who cannot tolerate beta-lactams.5,13

Late LD can often be treated with the same antibiotics used in earlier stages of disease. For instance, Lyme arthritis without evidence of neurologic disease can be treated with doxycycline, amoxicillin, or cefuroxime, all given orally for 28 days. If joint swelling persists, retreatment with another 4 weeks of oral agents or 2 to 4 weeks of intravenous ceftriaxone is advisable. Symptomatic treatment may also be used, including nonsteroidal anti-inflammatory medications, intra-articular injection of corticosteroids, or disease-modifying antirheumatic drugs. Late neurologic Lyme can be treated with intravenous ceftriaxone for 2 to 4 weeks, with retreatment not recommended unless relapse is evident by reliable objective measures.

Many treatment modes are not recommended by the IDSA because of a lack of efficacy or supporting data or the potential to harm the patient. These include long-term antibiotics or multiple repeated courses of antibiotics, pulsed-dosing of antimicrobials, hyperbaric oxygen therapy, and specific nutritional supplements, among others.5,13
CHRONIC LD AND PLDS

Definition and Prevalence

The majority of patients treated for LD with recommended regimens fully recover, while patients with objective evidence of treatment failure are quite rare. Approximately 10% to 20% of patients continue to experience subjective symptoms after treatment, including headache, fatigue, memory, and concentration difficulties and musculoskeletal pain. The diagnosis of chronic LD has been applied to patients with these symptoms by a small minority of practitioners. The term chronic Lyme disease can be very confusing because it has been used to describe patients with varying presentations, including those with symptoms of unknown cause and no evidence of B. burgdorferi infection, those with a well-defined illness other than B. burgdorferi infection, and those with symptoms of an unknown cause and antibodies against B. burgdorferi, but no objective clinical findings. As a result of the confusion surrounding the term, most field experts do not support its use and instead use the term post-Lyme disease syndrome to describe the persistent subjective symptoms that some patients experience.

The IDSA has proposed a definition of PLDS, which differs from chronic LD because it requires that patients have documentation of appropriately treated prior LD and persistent subjective symptoms without other medical explanations. Debate continues regarding the true frequency of prolonged symptoms and their cause, especially in the public domain.

Several studies conducted at LD referral centers have demonstrated that the illness is often overdiagnosed. These studies found that, on average, only a third to a quarter of patients referred for LD actually had the disease. Also 50% to 60% of these patients had no past or present evidence of LD. The majority of patients referred to specialty centers were found to have rheumatologic or neurologic conditions or syndromes such as fibromyalgia and chronic fatigue syndrome. This overdiagnosis was the result of misinterpretation of test results, clinical diagnoses in patients with subjective symptoms, use of serologic testing in patients with low pretest probability of LD, and use of nonvalidated test methods. Some patients may have positive serology from other infectious or inflammatory diseases, asymptomatic seroconversion, or a previous episode of LD. Overdiagnosis has led to many unnecessary courses of antibiotics, increased costs to the health care system, and more patients attributing their chronic symptoms to PLDS.

Long-term Antibiotics

As a result of the belief by a minority of clinicians that symptoms may be caused by persistent active infection, many patients diagnosed with chronic LD have been treated for months to years with multiple antimicrobial agents. Several prospective, placebo-controlled clinical trials have evaluated the role of long-term antibiotics in treating PLDS. All studies required that participants had appropriate documentation of previous LD that was treated with recommended antibiotic regimens. The first 2 trials, published in 2001, examined the effect of long-term antibiotics on patients who experienced persistent pain, fatigue, or impaired cognitive function. The primary outcome in this trial was health-related quality of life, measured using standard instruments. The investigators found no significant difference on any outcome between the placebo and treatment groups.

In another study, Krupp et al examined the effects of an additional 28 days of intravenous ceftriaxone versus placebo in patients with persistent fatigue and self-reported cognitive impairment. Patients in the ceftriaxone group did show improvement in fatigue but no improvement in cognitive function. In 2008, Fallon et al published their trial investigating the effect of 10 weeks of intravenous ceftriaxone versus placebo on cognitive function in patients with objective memory impairment. Researchers found greater improvement in the ceftriaxone group at 12 weeks, but the groups had made similar gains by 24 weeks.

A significant rate of adverse events was noted in several of these studies. In the Fallon et al trial, 24% of patients experienced severe adverse events related to ceftriaxone, including thromboemboli, allergic reactions, and cholecystitis. One observational study found that 19 of 200 patients treated with long-term intravenous antibiotics for PLDS experienced serious adverse events. The overuse of antibiotics contributes to the growing problem of antibiotic resistance.
The researchers conducting these studies concluded that additional antibiotics are not recommended for the treatment of PLDS because of the lack of efficacy and the risk of serious complications.

Although no studies have demonstrated a benefit in prolonging antibiotic treatment beyond 1 month for LD, there are many case reports of patients experiencing clinical benefit while on long-term antibiotic therapy. However, this type of evidence is highly subject to biases and does not hold the same weight as prospective, controlled clinical trials when assessing the benefit or risk of a specific treatment and making treatment recommendations. After reviewing the evidence, the IDSA found, in both their 2006 guidelines and 2010 review, that antibiotics are not recommended in patients experiencing more than 6 months of subjective symptoms who were previously treated with a recommended antibiotic regimen.

**FURTHER RESEARCH**

With all that has been discovered about LD and its pathogenicity and treatment, some questions still remain. Future research evaluating whether subjective symptoms attributed to PLDS are truly more common among those with a history of LD than the general population will help clarify whether these symptoms are related to this or another disorder. Because current research has not supported the use of long-term antibiotics in patients with PLDS, studies investigating non-antimicrobial treatments are needed.

**IMPLICATIONS FOR PRACTICE**

Infection prevention is the most effective way to decrease the morbidity associated with LD. NPs are in a key position to educate patients about ways to reduce exposure to tick-borne illnesses. Patients should be advised to avoid wooded or bushy areas and to use a repellant containing at least 20% DEET on their skin and products containing permethrin on their clothing. It is also important to shower soon after coming indoors and to check the entire body, clothing, and pets for ticks.

After a tick bite, routine use of antibiotic prophylaxis or serologic testing is not recommended. However, a single dose of doxycycline 200 mg can be given if all of the following criteria are met: the tick can be reliably identified as an *I. scapularis* tick, it has been attached for at least 36 hours, prophylaxis can be given within 72 hours of the time the tick was removed, at least 20% of ticks in the local region are infected with *B. burgdorferi*, and doxycycline is not contraindicated.

Regardless of a clinician’s views concerning chronic LD, it remains true that thousands are suffering from chronic symptoms that cannot be explained by current medical science. The NP in endemic areas is bound to encounter patients with early LD, as well as patients with chronic symptoms who attribute these symptoms to it. It is imperative to thoroughly evaluate any patients with chronic symptoms for medical conditions that may explain their situation. Collaboration with specialists is often necessary for a complete evaluation. Patients who believe they have chronic LD should be informed of the current evidence and recommendations by medical societies. It is especially important for the clinician to maintain open communication, patience, and empathy and not rush to judgment.

**References**


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