Lyme Disease: Diagnosis, Treatment, and Prevention

Evidence-based strategies for nurses.

ABSTRACT: Lyme disease is recognized as the most common vector-borne disease in the United States. Surveillance data indicate both increasing numbers of Lyme disease cases and geographic expansion of areas where the causative spirochete, *Borrelia burgdorferi*, can be found. With prompt diagnosis and appropriate treatment in the acute stage, most patients will recover fully. Without treatment, however, the infecting pathogen remains within the body, often producing long-term complications, including musculoskeletal, neurologic, and cardiovascular effects. The authors describe early and late manifestations of Lyme disease, the appropriate use of diagnostic tests, the recommended treatment, and strategies for preventing tick-borne diseases nurses can share with patients.

Keywords: diagnosis, Lyme disease, prevention, treatment

A healthy 26-year-old man presented to his primary care provider for evaluation of a rash on his neck. He had removed a tick from that area a few days earlier. (This case is a composite based on our experience.) He suspected that the tick had attached two weeks ago, when he was fishing with friends in East Tennessee. He said he had experienced no nausea, vomiting, fever, chills, malaise, headache, pain, or itching. He reported no history of hospitalization or allergies and said he took no medications. Examination revealed a discreet nontender lesion measuring 5 × 4 cm. It appeared as flat, homogenous erythema with no central clearing. His lymph nodes were not palpable, and he was discharged without a diagnosis.

The patient returned to the clinic three weeks later reporting malaise and joint pain, particularly in his knees. He explained that the rash had increased in size since his first visit but was now resolved. He asked whether he could have contracted Lyme disease from his tick bite. His primary care provider ordered a complete blood count (CBC) with differential, a complete metabolic panel, an enzyme immunoassay (EIA), and Western blot analyses to determine the presence of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies. Results from his CBC, metabolic panel, and EIA were normal. Since his EIA was negative, Western blot IgG and IgM analyses were not performed in accordance with laboratory protocol. The patient was told he did not have Lyme disease because his laboratory results were normal and Lyme disease is not endemic to East Tennessee.

One month later—that is, almost two months after he discovered the tick bite—he continued to experience pain and swelling in his knees, as well as fatigue, anorexia, and memory loss. He decided to obtain a second opinion from a Lyme specialist. This examination revealed that results of both his EIA and IgG analysis were positive. He was treated with a 28-day course of doxycycline 100 mg by mouth twice daily

Various presentations of the Lyme disease rash (clockwise from bottom left): early disseminated Lyme disease; two examples of the classic bull's eye or target rash; and an expanding red lesion with a central crust. Photos courtesy of Bernard Cohen.

and naproxen 500 mg by mouth every 12 hours. His symptoms improved after treatment but did not resolve until he was treated parenterally for Lyme arthritis with ceftriaxone 2 g IV daily for two weeks, to which he responded favorably.

More than 22,000 confirmed cases and nearly 9,000 probable cases of Lyme disease were reported to the Centers for Disease Control and Prevention (CDC) by state health departments and the District of Columbia in 2012.[1] However, based on testing data reported by clinical laboratories and medical claims information, Hinckley and colleagues estimated that 240,000 to 444,000 patients in the United States tested positive for Lyme disease in 2008.[2] Nurses may encounter patients with tick-borne illnesses in primary care, public health settings, EDs, infusion centers, and acute care settings. Prompt diagnosis and treatment are crucial to good outcomes, as most patients treated with appropriate antibiotics in the early stages of Lyme disease recover rapidly and completely. This article describes the clinical features of Lyme disease, the appropriate use of diagnostic tests, the recommended treatment, and strategies for preventing tick-borne diseases nurses can share with patients.

ETIOLOGY AND EPIDEMIOLOGY

Lyme disease is a multisystem zoonosis caused by the spirochetal microorganism *Borrelia burgdorferi* and transmitted by ticks of the *Ixodes ricinus* species complex.[3] Specifically, it is transmitted to humans in the United States by two species of blacklegged deer ticks: *I. scapularis*, in the Northeast, Mid-Atlantic, and North Central regions, and *I. pacificus*, in the Pacific Coast region.[3,4]

Lyme disease, which is now recognized as the most common vector-borne disease in the United States,[3,4] gets its name from the small town of Lyme, Connecticut, where in 1975 several cases of pediatric arthritis were diagnosed and reported to the state's department of health. Although the majority of cases are reported from states in the Northeast, North Central, and Pacific Coast regions,[4] recent surveillance data indicate both increasing numbers of cases and geographic expansion of areas where *B. burgdorferi* can be found.[4,5] When the 1998 distribution map of *B. burgdorferi* was updated based on 2015 data, primary vectors were identified in 49.2% of the counties in 43 states, representing a 44.7% increase in the number of counties recording their presence over a 17-year period.[4]

Table 1. Lyme Disease Treatment Recommendations from the Infectious Diseases Society of America[11]

Recommendation	Strength of Recommendation–Quality of Evidence[a]
Patients with a known tick bite in the absence of a rash	
To prevent Lyme disease, oral doxycycline may be offered to adults in a single 200-mg dose and to children ≥ 8 years at a dose of 4 mg/kg up to a maximum dose of 200 mg when the following criteria are met: • *Ixodes scapularis* tick attached for a minimum of 36 hours • treatment started within 72 hours of tick removal • infection rate > 20% in the locale where the tick bite occurred • doxycycline is not contraindicated	B-I
Patients with the characteristic erythema migrans rash	
For adults: • doxycycline 100 mg by mouth twice daily for 10–21 days, *OR* • amoxicillin 500 mg by mouth three times daily for 14–21 days, *OR* • cefuroxime axetil 500 mg by mouth twice daily for 14–21 days	A-I
For children ≥ 8 years: • doxycycline 4 mg/kg by mouth daily in two divided doses to a maximum of 100 mg per dose	A-II
For children < 8 years: • amoxicillin 50 mg/kg by mouth daily in three divided doses to a maximum of 500 mg per dose, *OR* • cefuroxime axetil 30 mg/kg by mouth daily in two divided doses to a maximum of 500 mg per dose	A-II
Patients with disseminated infection	
For Lyme meningitis and other manifestations of acute neurologic Lyme disease in adults: • ceftriaxone 2 g IV once daily for 10–28 days, *OR* • cefotaxime 2 g IV every 8 hours for 10–28 days, *OR* • penicillin G 18–24 million U IV daily in divided doses every 4 hours for 10–28 days, *OR* • if intolerant of β-lactum antibiotics, doxycycline 200–400 mg by mouth daily in two divided doses for 10–28 days	B-I
For Lyme meningitis and other manifestations of acute neurologic Lyme disease in children: • ceftriaxone 50–75 mg/kg IV daily in a single dose to 2 g maximum, *OR* • cefotaxime 150–200 mg/kg IV daily in three to four divided doses to a maximum of 6 g daily, *OR* • penicillin G 200,000–400,000 U/kg IV daily in divided doses every 4 hours to a maximum of 24 million U daily, *OR* • if ≥ 8 years, doxycycline 4–8 mg/kg by mouth daily in two divided doses to a maximum of 100–200 mg per dose	 B-I B-II B-I B-II
For cardiac complications, such as atrioventricular heart block and myopericarditis: • oral or parenteral antibiotic therapy for 14–21 days, with hospitalization and continuous monitoring of symptomatic patients advised	B-III
For Lyme arthritis in adults without evidence of neurologic disease: • doxycycline by mouth for 4 weeks, *OR* • amoxicillin by mouth for 4 weeks, *OR* • cefuroxime axetil by mouth for 4 weeks • If arthritis persists, a second 4-week course of oral antibiotics or a 2-to-4-week course of ceftriaxone IV may be necessary.	 B-I B-I B-III B-III
For Lyme arthritis in children without evidence of neurologic disease: • amoxicillin 50 mg/kg by mouth daily in three divided doses to a maximum of 500 mg per dose, *OR* • cefuroxime axetil 30 mg/kg by mouth daily in two divided doses to a maximum of 500 mg per dose, *OR* • if ≥ 8 years, doxycycline 4 mg/kg by mouth daily in two divided doses to a maximum of 100 mg per dose	 B-I B-III B-I
Patients with persistent posttreatment manifestations	
Antibiotic retreatment for patients with persistent posttreatment manifestations of Lyme disease is not recommended.	E-I

[a] These rankings are from the Infectious Diseases Society of America–U.S. Public Health Service Grading System (see Table 2).

Seasonality. In the United States, the risk of human infection with Lyme disease is greatest in late spring and summer, when people spend more time outdoors and the nymphal *I. scapularis* ticks seek hosts.[3, 6] Humans are most often infected through the bites of nymphs because they are small (about the size of a poppy seed) and profuse.[3, 6] Uninfected when they hatch from eggs, ixodid ticks require one blood meal in each subsequent life stage—larva, nymph, and adult. After hatching, they acquire *B. burgdorferi* by feeding on an infected host, usually a small mammal or bird.[3] When an infected tick takes a blood meal, the spirochetes increase in number and migrate to the tick's salivary glands, a process that occurs over several days.[7] For this reason, transmission of *B. burgdorferi* requires at least 36 hours of attachment,[3] underscoring the importance of showers and tick checks after exposure.

Coinfection. Notably people living in the northeastern and midwestern United States are not only at increased risk for infection with *B. burgdorferi*, but also for coinfection with *Babesia microti* and *Anaplasma phagocytophilum*, which are also transmitted by *I. scapularis*.[8] In patients with more severe symptoms of Lyme disease than those typically seen with *B. burgdorferi* infection alone (for example, a high-grade fever lasting more than 48 hours despite antibiotic treatment for Lyme disease; recurrent fever; or unexplained leucopenia, thrombocytopenia, or anemia), diagnostic testing for coinfection with these two pathogens should be considered.[7, 9]

CLINICAL PRESENTATION

In the early or acute stage of Lyme disease, the infection is localized to the skin and its most common clinical manifestation is erythema migrans, a rash that occurs in 60% to 90% of North American cases.[3] Typically, the rash develops three to 14 days after a tick bite at the site of the bite—often a skin crease in the axilla, groin, or popliteal fossa, or on the back or abdomen.[3, 9] It often appears as a macule or papule that is pale red to dark purple in color and expands over a period of days to form a lesion of at least 5 cm at its largest diameter.[10, 11] Size may be useful in identifying the characteristic rash since it is typically larger than that of a local inflammatory reaction to a tick bite, with rashes as large as 70 cm in diameter having been reported.[10]

Variations in the rash. Often assumed to exhibit central clearing, causing it to resemble a bull's eye or target, the Lyme rash is commonly homogenous in color and pattern, with central clearing more likely to occur the longer it persists.[10, 11] Approximately 20% of patients present with multiple lesions, suggesting hematogenous dissemination from the site of the bite.[10, 11] The rash or lesions may be accompanied by flu-like symptoms, such as fatigue, headache, muscle aches, joint pain, lymphadenopathy, stiff neck, and

Table 2. The Infectious Diseases Society of America–U.S. Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines

Category, Grade	Definition
Strength of recommendation	
A	Strongly in favor
B	Moderately in favor
C	Optional
D	Moderately against
E	Strongly against
Quality of evidence	
I	Evidence from ≥ 1 properly randomized controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time series studies; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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fever.[3, 9, 12] Prompt diagnosis is important because most patients who are treated appropriately at this stage will recover fully.[10] Without treatment, the Lyme disease rash resolves spontaneously within about four weeks, but the infecting pathogen remains within the body, often producing neurologic and cardiovascular effects.

Late Lyme disease sequelae resulting from bacterial dissemination to extracutaneous sites may be prevented if oral antibiotic treatment is initiated in the acute stage.[7, 13] In the United States, 32% of patients diagnosed with Lyme disease develop arthritis.[3] Generally thought to be mediated by the immune response to the spirochete in the joint, Lyme arthritis

Guidelines for Preventing Lyme Disease[29]

To prevent exposure:

- Avoid walking in wooded areas with tall grass and low brush.
- Walk in the center of trails.
- Wear light-colored clothing on which ticks are more easily detected.
- Wear long trousers and tuck them into socks. Wear long sleeves.
- Use repellants that contain 20% to 30% DEET (N,N-diethyl-meta-toluamide) on exposed skin for protection that lasts up to several hours. Avoid applying DEET to hands, eyes, and mouth.
- For children:
  - Choose a repellant that contains no more than 10% to 30% DEET.
  - Do not apply more than once a day.
  - Do not use on the face, under clothing, on cuts or irritated skin, or on the hands of young children.
  - DEET is not recommended for infants younger than two months old.
- Treat clothing, boots, and tents with products containing 0.5% permethrin or purchase pretreated clothing.
- Have pets wear tick collars and inspect them frequently.

After possible exposure:

- Bathe or shower as soon as possible after coming indoors, preferably within two hours, to wash off and remove ticks.
- Conduct a full-body tick check upon return from tick-infested areas.
- Look for what may appear to be a new freckle or a speck of dirt.
- Parents should check children for ticks under the arms, in and around the ears, in the belly button, behind the knees, around the waist, in the hair, and between the legs.
- Examine camping gear and pets. Ticks can enter the home on clothing and pets.
- Brush pets regularly using a tick comb after they have spent time outdoors in grassy or wooded areas.
- Tumble dry clothes for 10 minutes in a dryer on high heat. If washing is required, use hot water.

If a tick is found:

- Remove ticks with tweezers or one of several tick removal devices applied near the point of attachment.
- Pull upward with steady, even pressure.
- When using tweezers, avoid twisting or jerking the tick.
- Avoid folk remedies; hot matches, petroleum jelly, soap, or nail polish do little to encourage a tick to detach.
- After removing the tick, thoroughly clean the bite area and your hands with soap and water or rubbing alcohol.
- Save the tick in a bottle of alcohol if you need it later for identification.
- If you develop a rash or fever within two to 30 days after removal of the tick, see a health care provider. Be sure to report your tick bite, when it occurred, and where you were most likely exposed to the tick.

may manifest weeks to years (six months on average) after Lyme disease onset, with pain and swelling in one or more of the large joints, predominantly the knee.[11, 12, 14] Approximately 12% of patients with Lyme disease who are not promptly treated develop neurologic manifestations, the most common being facial nerve palsy.[3] Approximately 1% will develop a cardiac complication, typically an atrioventricular block.

DIAGNOSING LYME DISEASE

Lyme disease diagnosis requires a careful history, focused on a known tick bite or potential exposure to ticks in endemic areas—through participation in outdoor activities, contact with indoor–outdoor pets, or having a bird feeder in the yard or an outdoor dining area[15]—as well as the evolving appearance of clinical symptoms. Patients with a known tick bite in the absence of rash should be treated with antibiotics effective against *B. burgdorferi* without additional diagnostic testing, provided that an *I. scapularis* tick was attached for at least 36 hours, the rate of ticks infected with *B. burgdorferi* is at least 20% in the area of exposure, treatment can start within 72 hours of tick removal, and there is no contraindication to the antibiotic treatment.[11] *B. burgdorferi*, like most spirochetes, produces antibodies, so when symptoms are less clear but Lyme disease is suspected, laboratory testing is recommended.[11, 16]

Testing. The CDC recommends a two-step laboratory testing process.[11, 16] The first step involves a quantitative screening with an EIA. If the results are negative, no further testing of the serum sample is required; if results are positive or indeterminate for antibodies, the sample is retested with separate IgM and IgG immunoblots.[16, 17]

Obtaining serologic tests at the time of a tick bite is not useful. There is a positive association between duration of infection and sensitivity of the serologic tests, which are usually negative during the first weeks of *B. burgdorferi* infection because detectable antibody responses have not yet developed.[7] Serologic testing in the acute phase may be paired with serologic testing in the convalescent phase 30 days after initial testing.[18]

As with all infections, the initial antibodies to *B. burgdorferi* are in the IgM class and, as the immune response matures, there is a shift to IgG antibodies. If infection has persisted for four weeks or more, the IgG immunoblot is usually positive, though some patients treated for Lyme disease do not develop a measurable IgG response following antibiotic treatment.[19] Once a patient is seropositive, elevated IgG titers can persist for years.[13]

CONTROVERSIES IN TREATMENT

According to the clinical practice guidelines published by the Infectious Diseases Society of America (IDSA), which are reflected in the treatment guidelines of the CDC, a 14-day course of oral antibiotics is usually sufficient to cure the majority of Lyme disease cases diagnosed in the early stages.[11, 20] (See Tables 1 and 2.[11]) Some health science professionals, however, disagree, pointing to studies suggesting that 10% to 20% of patients who were diagnosed with the characteristic Lyme disease rash and received recommended antibiotic treatment continue to have symptoms such as fatigue, arthralgia, headaches, irritability, and difficulty with memory and concentration long after treatment.[21]

Approximately 12% of patients with Lyme disease who are not promptly treated develop neurologic manifestations.

Posttreatment Lyme disease syndrome is often used to describe patients who remain symptomatic for months to years after completing the recommended antibiotic therapy.[11] Although the exact cause of this syndrome is unknown, many experts posit that the lingering symptoms result from residual damage to the tissues and immune system.[22] A competing theory holds that posttreatment symptoms are attributable to

Lyme Disease Resources

Centers for Disease Control and Prevention
Tickborne Diseases of the United States: A Reference Manual for Health Care Providers
www.cdc.gov/lyme/resources/TickborneDiseases.pdf

Lyme Disease: What You Need to Know
www.cdc.gov/lyme/resources/brochure/lymediseasebrochure.pdf

Lyme Disease webpage
www.cdc.gov/lyme/index.html

Johns Hopkins Arthritis Center
Lyme disease webpage
www.hopkinsarthritis.org/arthritis-info/Lyme-disease

National Institute of Allergy and Infectious Diseases
Lyme disease webpage
www.niaid.nih.gov/diseases-conditions/lyme-disease

the original infection and represent treatment failure or persistent infection with *B. burgdorferi*, requiring months to years of IV antibiotic therapy, oral antibiotic therapy, or both.[13, 23] Microbiological studies, however, have found no convincing evidence of the latter. Four randomized, placebo-controlled trials sponsored by the National Institutes of Health found no evidence that the benefit of retreatment with antibiotics exceeded the risks.[7] For this reason, the IDSA, CDC, American College of Rheumatology, American Academy of Pediatrics, and American College of Neurology do not recommend prolonged courses of antibiotics, citing a lack of biologic evidence for the existence of *B. burgdorferi* infection among patients after receipt of the recommended treatment regimens.[11, 24, 25]

Transmission of *B. burgdorferi* requires at least 36 hours of attachment, underscoring the importance of showers and tick checks after exposure.

Competing guidelines. In 1999, an interdisciplinary group of health science professionals established the International Lyme and Associated Diseases Society (ILADS), a group that regards Lyme disease as potentially chronic.[26] In 2004, the ILADS published its own Lyme disease management guidelines, emphasizing individualized treatment based on disease severity, quality of life impairments, and potential causes of relapse or symptom progression, including infection with other tick-borne diseases.[23] The 2004 ILADS guidelines were updated in 2014; both versions advocate prolonged antibiotic therapy for chronic Lyme disease.[23, 26] A lack of firm data on the incidence, prevalence, and pathogenesis of posttreatment Lyme disease, as well as controversy over diagnosis and treatment have frustrated health care providers and their patients.[7]

In 2008, two years after the IDSA had addressed the issue of chronic Lyme disease, citing "no convincing biologic evidence" of *B. burgdorferi* infection among patients who had received recommended antibiotic treatment,[11] the office of the attorney general of Connecticut challenged the IDSA guidelines and the IDSA voluntarily committed to a one-time structured guideline review to "put to rest any questions about them."[27] In 2009, a committee overseen by a jointly appointed ombudsman conducted the review and unanimously upheld the 2006 IDSA guideline recommendations.[27]

A summary of the ILADS guidelines (available on the National Guideline Clearinghouse website at www.guideline.gov/summaries/summary/49320) provides quality-of-evidence ratings for each recommendation. All recommendations in the guidelines were judged to be based on "very low-quality evidence." The panel, therefore, based its assessment of the strength of each recommendation on "the extent to which the risk–benefit assessment favored a particular course of action and aligned with values of most patients."[28] The only guideline recommendation that was given a "strong" rating was the one advising clinicians to "discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease," providing "patient-specific risk–benefit assessments for each treatment option" that include information about *Clostridium difficile* infection "and the preventative effect of probiotics."[28]

CONCLUSIONS AND RECOMMENDATIONS

Guidelines from both the IDSA and the ILADS agree that patients are likely to have better outcomes if their Lyme disease is diagnosed and treated promptly.[11, 23] The patient described in the opening scenario apparently had a Lyme disease rash at the site of a tick bite. If the possibility of Lyme disease had been recognized when the patient presented to his health care provider, he could have been prescribed a 10-day course of oral doxycycline and probably would have recovered completely. However, since the provider did not recognize the rash, the patient was discharged with no information about the signs and symptoms of tick-borne diseases. If he had returned to the clinic when the rash expanded, it's possible the rash would have been diagnosed and he could have then been prescribed a 10-to-21-day course of oral doxycycline. At the patient's insistence, however, the provider ordered a serologic assay, which is seldom positive in the acute disease stage. It would have been appropriate to retest the patient two to six weeks after testing the original blood sample, but instead the provider misinterpreted the results of the serologic assay and missed the diagnosis because he did not believe Lyme disease to be endemic to the area in which the patient received the tick bite. By the time the patient sought a second opinion from a Lyme disease specialist, he had been symptomatic for more than six weeks. The repeat IgG immunoblot analysis was positive, and he was diagnosed and treated for Lyme arthritis, which eventually responded to parenteral therapy.

The increasing risk of human exposure to tick-borne disease underscores the need for patient education to prevent human Lyme disease and other tick-borne diseases (see *Guidelines for Preventing Lyme Disease*[29] and *Lyme Disease Resources*). A safe and effective vaccine would provide an important resource in prevention. A French company has developed a vaccine that has shown efficacy in preclinical models, but it is only in Phase 1 trials in the United States and Belgium.[30]

The education of health care providers regarding the identification of ixodid ticks, the clinical features of Lyme disease, the recommended use and interpretation of diagnostic tests, and the benefits and drawbacks of the recommended treatment regimens is vital to providing high-quality patient care. ▼

For one additional continuing nursing education activity on Lyme disease, go to www.nursingcenter.com/ce.

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