Lyme borreliosis is a tickborne infection caused by the spirochete *Borrelia burgdorferi* sensu lato and is the most prevalent tickborne infectious disease in the United States. The spirochete (spiral-shaped bacterium) *B. burgdorferi* is transmitted to humans primarily by the black-legged tick or deer tick, *Ixodes scapularis*, on the east coast. On the west coast, the primary vector is the western black-legged tick (*Ixodes pacificus*). According to the Centers for Disease Control and Prevention’s (CDC) 2007 data, 27,444 cases of Lyme disease were reported, with a national average of 9.1 cases per 100,000 persons.\(^1\)

Residents of the coastal northeast, northwest California, and the Great Lakes region are at highest risk. In the 10 states where Lyme disease is most common, the average was 34.7 cases per 100,000 persons.\(^1\) The incidence of Lyme disease is on the rise; the CDC reported that the number of cases of Lyme disease has doubled in the United States since 1991 and stated that these numbers are probably underestimated.\(^2\)

**Pathology**

Typically, the *Ixodes* tick must feed for at least 36 hours for transmission of the bacterium to occur. *B. burgdorferi* enters the skin at the site of the tick bite, and then may spread through the lymph or blood. Tick bites often go unnoticed because of the small size of the tick in its nymphal stage. Some individuals infected with the *B. burgdorferi* spirochete do not show any signs of Lyme disease. Generally, there are 3 distinct stages of the disease process, with unique symptoms associated with each phase.

**Early Localized Infection**

Approximately 75% of infected patients develop a circular rash known as erythema migrans. The rash begins at the site of the tick bite, usually within 3–30 days, and gradually expands. The center of the rash may clear as it enlarges, resulting in a “bull’s-eye” appearance. Some patients develop additional erythema migrans lesions in other areas of the body after several days. Erythema migrans does not occur in all patients with Lyme disease. In patients who do not get the rash, the first sign of bacterial infection can be symptoms of second- or third-stage Lyme disease.

**Early Disseminated Infection**

The second stage occurs days to weeks after the tick bite as the bacteria spread throughout the body. Infected individuals may experience symptoms of fatigue, chills, fever, headache, swollen lymph nodes, myalgias, and arthralgias. Neurologic, musculoskeletal, or cardiovascular symptoms and multiple erythema migrans lesions may also develop. More specifically, individuals may present with facial muscle paralysis (Bell’s palsy), peripheral neuropathy, meningitis with severe headaches and neck stiffness, and abnormal heartbeat. Arthritis may begin with swelling, stiffness, and pain. Usually, only one or a few joints become affected, most commonly the knees. The rash generally resolves in about 1 month without treatment.

**Late Disseminated Infection**

The late stage can occur weeks, months, or even years after initial infection in patients who did not receive antibiotic treatment for early Lyme disease or in individuals whose treatment did not eliminate the bacteria completely. Approximately 60% of patients with untreated infection will begin to have intermittent arthritis, with severe joint pain and swelling, with the large joints most often affected. Chronic arthritis develops in 10%–20% of untreated infected individuals.\(^3\)

In addition, up to 5% of untreated patients may develop chronic neurologic complaints featuring motor and sensory
nerve damage and brain inflammation months to years after infection. Entry of spirochetes into the central nervous system (CNS) may result in a severe inflammatory reaction and produce proinflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor–alpha (TNF–α). Symptoms of neuropathy or encephalopathy may include shooting pains, numbness or tingling in the hands or feet, and problems with concentration and short-term memory loss. Lyme disease may become chronic with involvement of the central and peripheral nervous systems, and ophthalmic, cardiac, and musculoskeletal defects. Patients may present with rheumatoid arthritis (RA); neurologic impairment with memory and cognitive loss, anxiety, and depression; cardiac disease such as myocarditis and endocarditis causing palpitations, pain, and bradycardia; and severe chronic fatigue and sleep disturbance. Currently, the exact cause of these chronic symptoms is not known. There is some evidence that the chronic symptoms may result from an autoimmune response.5

Lyme and Autism
One theory suggests there may be an association between Lyme disease and autism. This theory is supported by numerous clinical findings such as case reports of mothers with Lyme disease whose children develop autism spectrum disorders; fetal neurologic abnormalities associated with tick-borne diseases; and symptom similarities between tick-borne diseases and autism spectrum disorders, with similar immune reactivity, temporal–lobe pathology, and brain imaging data. In addition, several studies of patients with autistic spectrum disorder showed positive testing for B. burgdorferi (20%–30%) and Mycoplasma (58%) with similar geographic distributions and reductions of autistic symptoms as a result of antibiotic treatment.6

Lyme Disease and Alzheimer’s Disease
There is some evidence linking B. burgdorferi infection with Alzheimer’s disease. B. burgdorferi has been isolated from beta-amyloid deposits of patients with Alzheimer’s disease. This research suggests that B. burgdorferi may persist in the brain and be associated with amyloid plaques. Researchers who conducted a study on this concluded that spirochetes, perhaps in an analogous fashion to Treponema pallidum, may contribute to dementia, cortical atrophy, and amyloid deposition seen in Alzheimer’s disease.7

The symptoms of the late chronic phase of Lyme disease have considerable overlap with other chronic conditions, often making diagnosis difficult. Chronic conditions such as chronic fatigue syndrome (CFS), fibromyalgia, and RA present similarly. In addition, co-infection frequently occurs, complicating the diagnosis.

Co-Infections
Co-infections are common with Lyme disease and complicate its diagnosis and presentation.

The intracellular protozoan Babesia microti is a tick-transmitted infection that may also be seen in Lyme disease infections.8 Babesia co-infection generally increases the severity of presenting symptoms, including: high fever; chills; generalized weakness; gastrointestinal (GI) symptoms such as anorexia, nausea, abdominal pain, vomiting, and diarrhea; anemia; muscle and joint pain; respiratory problems; and dark urine. Babesia infection may produce mild-to-severe hemolytic anemia and normal to slightly depressed leukocyte count, and may progress to disseminated intravascular coagulation, acute respiratory distress syndrome (ARDS), and heart failure.

Another co-infection seen with Lyme disease is another tickborne infection, Ehrlichia, such as E. chaffeensis and E. phagocytophila.9 Patients who have this rickettsial infection may present with fever, shaking chills, headache, muscle pain and tenderness, nausea, vomiting, abdominal pain, diarrhea, cough, and confusion. Ehrlichia infection may also cause mild-to-moderate transient hemolytic anemia, decreases in white blood cell count, elevated erythrocyte sedimentation rate (ESR), increased liver enzymes, and increased blood urea nitrogen (BUN) and creatinine within 1–3 weeks of exposure.

Chronic Lyme Disease
Chronic Lyme disease is a controversial issue, as many doctors and scientists disagree on whether it is a true medical condition. The term chronic Lyme disease is used to describe patients presenting with symptoms associated with post-Lyme disease but without objective signs of previous or current infection with B. burgdorferi, as well as patients who are classified as having post-Lyme disease syndrome. Post-Lyme disease syndrome is defined as continuing or relapsing generalized symptoms, including fatigue, musculoskeletal pain, and cognitive complaints in patients previously treated for Lyme disease. Currently, there are not consistent data showing that post-Lyme disease syndrome is caused by persistent infection with B. burgdorferi.10

Currently, the Infectious Diseases Society of America (IDSA) and the CDC do not support the diagnosis of chronic Lyme disease.11 Many experts believe that chronic Lyme disease is a misnomer, and this diagnosis is not based upon well-defined clinical criteria and validated laboratory studies, but solely on clinical judgment.12 However, the International Lyme and Associated Disease Society advocates that the IDSA’s refusal to recognize the possibility of chronic Lyme disease and need for additional therapy is based on biased research and is disturbing.13 They argue that chronic Borrelia infections are well-documented and that it would be illogical to assume that persistent symptoms in patients who are chronically ill with Lyme disease are not related
to active infection with *B. burgdorferi*. Furthermore, some states are proposing legislation to require insurance companies to pay for prolonged intravenous (IV) therapy to treat chronic Lyme disease.

The IDSA and CDC base their position on several studies that did not find prolonged antibiotic therapy effective for treating residual Lyme disease symptoms. One group of researchers conducted two randomized clinical trials for patients with well-documented, previously treated Lyme disease and who had persistent musculoskeletal pain, neurocognitive symptoms or dysesthesia, and fatigue. One group was seropositive for immunoglobulin (IgG) antibodies to *B. burgdorferi* at the time of enrollment and the other group was seronegative. The patients received either 2 g of IV ceftriaxone daily for 30 days, followed by 200 mg of oral doxycycline daily for 60 days, or matching IV and oral placebos. In this study, treatment with IV and oral antibiotics for 90 days did not reduce Lyme symptoms better than did placebo.

Another randomized placebo-controlled trial evaluated the benefit of 28 days of IV ceftriaxone or placebo in patients with Lyme disease with persistent severe fatigue lasting 6 or more months after antibiotic therapy. Patients assigned to ceftriaxone had reduction of disabling fatigue compared with the placebo group, but there was not any benefit observed for cognitive function or the laboratory measure of persistent infection. In addition, adverse events were reported. Overall, the study authors concluded that additional antibiotic therapy for post-Lyme disease syndrome had considerable risk and was not supported by the evidence.

In another study, patients with well-documented Lyme disease with at least 3 weeks of prior IV antibiotics; current positive IgG Western blots; objective memory impairment; and marked levels of fatigue, pain, and impaired physical functioning were evaluated for additional antibiotic therapy efficacy. Patients were given 10 weeks of double-masked treatment with IV ceftriaxone or IV placebo and then no antibiotic therapy. IV ceftriaxone therapy resulted in short-term cognitive improvement at week 12 for patients with post-treatment Lyme encephalopathy. However, the week 24 evaluation showed that a relapse in cognition occurred after the antibiotic was discontinued. In addition, adverse events were reported in 26% of the patients in the IV ceftriaxone group. The authors concluded that, because of the limited duration of the cognitive improvement and the risks involved, 10 weeks of IV ceftriaxone was not an effective strategy for producing cognitive improvement.

**Laboratory Testing**

Diagnosis is usually made clinically based on history of possible exposure to ticks, symptoms, and physical signs, such as erythema migrans, facial palsy, or arthritis. Laboratory tests are not generally recommended patients who have erythema migrans or for patients without Lyme disease symptoms. The CDC recommends a two-step approach for laboratory testing for Lyme disease, including an initial screening test, such as an enzyme-linked immunosorbent assay (ELISA) with high sensitivity, followed by an immunoblot with high specificity.

**ELISA and Immunofluorescent Assay**

First, an ELISA or immunofluorescent assay (IFA) is performed. These tests are designed to be very sensitive, meaning that almost everyone with Lyme disease will test positive. The Lyme ELISA test is intended for the quantitative detection of IgG and IgM antibodies in serum to *B. burgdorferi*. Titers of IgG are generally low during the first weeks of illness and peak within 3–6 weeks after onset. If the ELISA or IFA is positive or indeterminate (or equivocal), the Western immunoblot assay is used to confirm the results.

**Western Blot**

The Western immunoblot assay is used for confirmation of Lyme disease as this assay is specific, meaning that it will usually show positive results only if an individual is infected. Negative results on a Western blot suggest that the initial ELISA or IFA was a false-positive. The Western blot assay is a more reliable test, as it is able to exclude crossreactive antibodies and can measure peptide-specific antibodies. However, false-negative results will be obtained if antibodies are not present in the blood. The CDC does not recommend testing by Western blot without first testing patients with an ELISA or IFA.

**Polymerase Chain Reaction**

The polymerase chain reaction (PCR) test detects *Borrelia* DNA in blood, skin biopsies, or cerebral spinal fluid (CSF) and has proven to be quite sensitive. However, PCR has not yet been well-standardized, and measuring blood DNA requires the spirochete be released into the blood where the DNA can be detected, which does not occur reliably. Currently, the best use of PCR is for confirmation of the clinical diagnosis of suspected Lyme arthritis in patients who are IgG-immunoblot-positive.

**Additional Testing**

Some laboratories offer Lyme disease testing with questionable accuracy. These tests include urine-antigen tests, fluorescent antibody tests, high-resolution microscopy, and lymphocyte transformation tests. The CDC does not currently recommend these tests.

**Testing Limitations**

Current testing for Lyme disease is unreliable. Lack of sensitivity of the assays and interlaboratory variability due to a lack of standardization and poor evaluation criteria regarding sensitivity and specificity are common problems. To demonstrate this, researchers sent one aliquot of serum from each of 9 patients with histories of Lyme disease to 9 reference laboratories, including national, university, state, and local hospital laboratories, with a second aliquot of the original serum submitted 2 weeks later. There was large variability in both inter- and intralaboratory results. For example, one laboratory detected the antibody to *B. burgdorferi* (IgG or IgM) in 18 of
18 specimens, while another laboratory detected the antibody in only 8 of the 18 specimens.21 However, the reliability of laboratory testing has increased since these studies.

In addition, the *B. burgdorferi* spirochete has numerous unique antigens and is able to vary its outer surface proteins to avoid detection by the immune system. This antigenic variation makes detecting the presence of the bacterium difficult and many tests unreliable. Serology testing for antibodies against *Borrelia* antigens also shows crossreactivity with other microorganisms. Thus, it is recommended that the results of serologic testing should not be relied on as the sole criterion in making the diagnosis of Lyme disease.

**Conventional Treatment**

For most patients with Lyme disease, antibiotic therapy is curative. Typically, doxycycline for adults and children over age 8 or amoxicillin is given for 2–4 weeks for patients with early stage Lyme disease. As an alternative, cefuroxime axetil, or erythromycin, can be used. Late or severe disease requires IV ceftriaxone (Rocephin) or penicillin G. Single-dose doxycycline (200 mg orally) may also be used as prophylaxis, after a tick bite in an endemic area, for example. Doxycycline also produces good activity against most species of *Mycoplasma* and *Ehrlichia*, with good penetration into the CNS. Patients with chronic symptoms that are unresponsive to antibiotics may be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.

**Natural Treatments**

Research regarding natural therapies for Lyme disease is scarce. However, there is anecdotal evidence supporting the use of *Uncaria tomentosa* (cat’s claw) for Lyme disease. In addition, clinicians have reported benefit from supportive measures to complement antibiotic therapy.

**Cat’s Claw**

Cat’s claw is used medicinally for antioxidant, anti-inflammatory, immunostimulant, and antiviral activity. Constituents in cat’s claw known as pentacyclic oxindole alkaloids (POAs) have immunomodulatory effects, enhancing phagocytosis and increasing lymphocyte activity. However, cat’s claw also contains tetracyclic oxindole alkaloids (TOAs), which antagonize the positive effect of the POAs.22

Samento, also known as TOA-Free Cat’s Claw, (NutraMedix LLC, Jupiter, Florida), is a commercially available form of the herb and has been used for treating Lyme disease. C-Med® (M.W. International, Inc., Hillside, New Jersey), another proprietary extract of cat’s claw, has been shown to increase several white blood cells, including B and T lymphocytes, natural killer (NK) cells, and granulocytes.23 In addition, the constituents known as quinovic acid glycosides, which are similar to the quinolone antibiotics, have produced antibacterial and immune stimulating activity.24 Cat’s claw has anti-inflammatory properties. It is believed that this activity is due to the ability of the herb to inhibit the production of the proinflammatory cytokine TNF-α, which is a critical mediator of inflammation and the immune response and which is elevated in patients with Lyme disease. Cat’s claw also inhibits the production of prostaglandin E2 (PG E2).25,26

Cat’s claw has been studied as a treatment for RA and osteoarthritis (OA). In a randomized, double-blind, placebo-controlled study, patients with RA and currently undergoing sulfasalazine or hydroxychloroquine treatment were evaluated for efficacy of cat’s claw supplementation. During the first 24 weeks, patients were treated with cat’s claw extract or placebo. In the second phase of the study, lasting 28 weeks, all of the patients were given the herb. At the end of the study, 24 weeks of treatment with the cat’s claw extract resulted in a significant reduction of the number of painful and swollen joints compared with placebo.27 This anti-inflammatory activity may be beneficial for patients with Lyme-associated arthritis.

**Additional Supplements**

Clinically, there are numerous other supplements that may provide benefit to patients with Lyme disease due to these supplements’ antimicrobial and/or anti-inflammatory activity. Despite a lack of conclusive research studies, doctors and patients have reported therapeutic benefits for various natural therapies. These supplements include:
• Urtica dioica (stinging nettles) is an herb used for its antimicrobial and anti-inflammatory properties. Nettles have been shown to decrease numerous proinflammatory cytokines. Research suggests that part of the anti-inflammatory effect of nettles extract may be due to its inhibitory effect on nuclear factor-kappaB (NFkB) activation. Other studies have shown that stinging nettles inhibit TNF-α, interleukin-6 (IL–6), and IFN-γ, all of which have been shown to be elevated in patients with Lyme disease. Researchers suggest that this inhibition of inflammatory cytokines is the mechanism by which stinging nettles can reduce inflammation in inflammatory joint diseases.

• Zingiber officinalis (ginger) root has antibiotic and anti-inflammatory activity. Studies have shown that ginger extract significantly inhibits the activation of TNF-α and cyclo-oxygenase-2 (COX–2) expression in human synoviocytes. In addition, ginger also suppresses leukotriene biosynthesis by inhibiting 5-lipoxygenase (5-LOX), as well as suppressing platelet thromboxane-B2 and PG E2. In addition, other research indicates that ginger is effective for reducing pain and swelling in OA and RA.

• Boswellia serrata (boswellia), also known as Indian frankincense, is an Ayurvedic botanical used for treating inflammatory disease. The resin from the plant contains pentacyclic triterpenes (boswellic acids) that produce much of this plant’s anti-inflammatory activity. The acids contained in boswellia inhibit the enzyme 5-LOX by binding to the enzyme, resulting in decreased leukotriene production. Boswellia has also reduced symptoms associated with OA.

• Glycyrrhiza glabra (licorice) has significant anti-inflammatory activity. Licorice extract has inhibited the proinflammatory cytokines interleukin IL–β, IL–6, and IL–8, and TNF-α responses of macrophages. Licorice also has antimicrobial activity against both gram-positive and gram-negative bacteria.

• Artemisia herba-alba has antibacterial and anti-inflammatory activity.

• Allium sativum (garlic) has potent antimicrobial activity. Allicin, one of the active constituents, has antimicrobial activity against a wide range of bacteria and has antiviral, antifungal, and antiparasitic properties.

• Echinacea purpurea (echinacea) has antimicrobial activity against various organisms and produces significant immune-modulating activity. Research also suggests that this herb may also have some anti-inflammatory properties, through inhibition of the COX and 5-LOX pathways. Echinacea species have also inhibited TNF-alpha release.

• Pycnogenol® (Pinus maritimus; Horphag Research, Geneva, Switzerland), a French maritime pine bark extract, has anti-inflammatory and antioxidant activity. Pycnogenol suppresses the TNF-alpha-induced activation of NFkB and inhibits the enzymatic activities of COX-1 and COX-2. Pycnogenol also had significant efficacy for treating arthritis symptoms in a study. This effect was likely to be due to anti-inflammatory activity, as levels of C-reactive protein (CRP), plasma free radicals, and fibrinogen were decreased in the study patients.

• Quercetin is a flavonoid used medicinally for its antioxidant and anti-inflammatory activity. Quercetin inhibits COX and 5-LOX enzymes, and inflammatory mediators such as leukotrienes and prostaglandins. Researchers have shown that quercetin suppresses gene expression and production of the proinflammatory cytokines TNF-α, IL-1β, IL-6, and IL-8, several of which have been shown to be elevated in patients with Lyme disease.

• Probiotics such as Lactobacillus acidophilus and Bifidobacterium spp. are recommended to decrease the growth of yeast and pathogenic bacteria that can occur with antibiotic therapy.

• Colloidal silver is a suspension of ultrafine, electrically charged silver particles in water. Inorganic silver compounds produce germicidal activity by binding to the reactive groups on proteins, leading to denaturation and precipitation. Topically, silver-treated wound dressings and creams have produced significant antimicrobial activity.

• Nutritional support for cognitive dysfunction such as Gingko biloba or l-acetyl-carnitine may also be helpful.

**Conclusion**

The incidence of Lyme disease is rapidly increasing in the United States. Although many patients are cured with standard antibiotic treatment, there are countless patients that are not and are in need of additional treatment. Long-term sequelae including severe fatigue and neurologic deficits surely make an impact on the quality of life of these patients. Clearly, research is needed to optimize diagnosis and treatment for this condition. In addition, the debate regarding the existence of chronic Lyme disease continues. Promising natural therapies such as cat’s claw may provide benefit for these patients.
References


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