



CIGNA MEDICAL COVERAGE POLICY

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**Subject Lyme Disease Treatment—
Antibiotic Treatment**

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Coverage Policy

Coverage for treatment of Lyme disease may be governed by state mandates.

CIGNA covers up to 28 days of intravenous antibiotic therapy as medically necessary for the treatment of Lyme disease when ANY of the following criteria is met:

- early Lyme disease with EITHER of the following:
 - neurological involvement manifested by meningitis or radiculopathy
 - third degree atrioventricular block
- late Lyme disease with EITHER of the following:
 - recurrent arthritis after administration of a complete course of oral antibiotics
 - central nervous system (CNS) or peripheral nervous system involvement
- Lyme arthritis and/or Lyme-related neurological conditions that have proved refractory to a full course of recommended oral antibiotic therapy.

CIGNA does not cover the use of ANY of the following treatments for Lyme disease because they are considered experimental, investigational or unproven for this indication (this list may not be all-inclusive):

- intravenous antibiotics for early Lyme disease in the absence of neurological involvement manifested by meningitis or radiculopathy, or third-degree atrioventricular block
- a course of intravenous antibiotics lasting longer than 28 days
- the use of prophylactic antibiotic therapy for individuals with no clinical findings indicative of Lyme disease
- repeated or prolonged courses of parenteral or oral antibiotics
- pulsed-dosing (i.e., dosing on some days but not others)

General Background

Lyme disease was first recognized in the United States in 1975, after an unusual outbreak of arthritis near Lyme, Connecticut. Lyme disease is caused by the spirochete *Borrelia burgdorferi*, which is spread through the bite of an infected tick. The black-legged tick (or deer tick), *Ixodes scapularis*, spreads the disease in the northeastern and north central United States, and the western black-legged tick, *Ixodes pacificus*, spreads the disease on the Pacific Coast. In general, the tick needs to be attached to a host 36–48 hours before the Lyme disease bacterium will be transmitted. Most humans are infected through the bite of an immature tick, known as a nymph. Nymphs are tiny, less than 2 mm, and difficult to see. Adult ticks can also transmit the disease, but they are much larger and more likely to be discovered and removed. *Ixodes* ticks are much smaller than common dog and cattle ticks. Lyme disease is the most common vector-borne disease in the United States (Bacon, et al., 2008). Cases are most common in northeastern and north central states and among persons aged 5–14 years. The CDC reports that in years 1992–2006, 248,074 cases were reported, of which 93% of cases were reported from the ten states where Lyme disease is considered endemic: Connecticut, Delaware, Rhode Island, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, and Wisconsin (Bacon, et al., 2008).

There are several approaches to Lyme disease prevention (CDC, American Academy of Pediatrics [AAP], 2000). These prevention methods include, but are not limited to, the following:

- minimize exposure to vector ticks in residential areas
- avoid heavily tick-infested areas
- wear light-colored protective clothing
- use insect repellents
- check frequently (daily) for ticks

In 2000, the AAP's Committee on Infectious Disease published recommendations on the prevention of Lyme disease. The guidelines note that routine use of antimicrobial agents to prevent Lyme disease after a deer tick bite, even in highly endemic areas, is not recommended. The AAP guidelines also note that serologic testing at the time of a recognized tick bite is not recommended. At the time of a tick bite, there is little or no chance that there are detectable antibodies to *Borrelia burgdorferi*.

In general, there are three stages of Lyme disease: early localized disease, early disseminated disease, and persistent or late disease (Hengge, et al., 2003). Early infection may be followed within days or weeks by disseminated infection that affects the nervous system, heart or joints, and then, within weeks or months, by late or persistent infection (Steere, 2001).

The diagnosis of Lyme disease should take into account history of possible exposure to ticks in areas where Lyme disease is known to occur; signs and symptoms of the illness; and results of blood tests used to detect whether the patient has antibodies to the Lyme disease bacterium. Laboratory tests must be interpreted in relation to the patient's recent medical history, signs and symptoms. The laboratory tests do not detect an infection until the body begins to produce measurable levels of antibodies to the Lyme disease bacterium, usually two to four weeks after the bite of an infected tick and, therefore, they may be falsely negative in patients with erythema migrans.

Early Lyme disease most often presents with a characteristic rash, erythema migrans or “bull’s eye” rash, which may be accompanied by nonspecific symptoms such as fever, chills, malaise, fatigue, headache, muscle and joint aches and swollen lymph nodes. Erythema migrans is a red circular patch that appears at the site of the tick bite, usually within three days to one month after the bite of an infected tick. The patch may then grow larger. There may be more than one patch, varying in size and shape. Common sites are groin, thighs, trunk and armpits. The center of the rash may clear as it enlarges, which results in the “bull’s-eye” appearance. The incubation period from infection to onset of symptoms is typically 7–14 days, but may be as short as three days or as long as 30 days. It is also possible that an individual will manifest only nonspecific symptoms and not have the rash.

Early disseminated disease occurs within days or weeks of the infection and may affect the nervous system, heart or joints (Steere, 2001). If Lyme disease is untreated or inadequately treated, the disease may progress to late or persistent infection.

Co-infection with other Tick-Borne Diseases

Co-infection may occur with Lyme disease. The Ixodes ticks that transmit the Lyme disease bacterium often carry, and may transmit simultaneously, other pathogens such as anaplasma phagocytophilum (previously referred to as Ehrlichia phagocytophila), which causes human granulocytic anaplasmosis (HGA) (which was previously referred to as human granulocytic ehrlichiosis [HGE]), and Babesia microti, which causes babesiosis (National Institute of Allergy and Infectious Diseases [NIAID]; Wormser, et al., 2006). Co-infection with these other infectious agents may interfere with the clinical diagnosis of Lyme disease. Co-infection should be considered in patients who exhibit more severe initial symptoms than are commonly observed with Lyme disease alone. In particular, these conditions should be considered with patients who have high-grade fever for > 48 hours, despite receiving antibiotic therapy for Lyme disease, or who have unexplained leucopenia, thrombocytopenia, or anemia.

Neurological Involvement

Symptoms of acute peripheral nervous system involvement in Lyme disease include radiculopathy, cranial neuropathy, and mononeuropathy multiplex. Central nervous system involvement may include lymphocytic meningitis and, rarely, encephalomyelitis. Cranial neuropathy is the most common manifestation of early neurologic Lyme disease, with seventh nerve palsy being the most common of the cranial neuropathies. It has been reported that early Lyme disease occurs in approximately 10–15% of untreated patients with Lyme disease in the United States, although recently it is thought the frequency is less (Wormser, et al., 2006).

Cardiac Involvement

Within several weeks from the onset of Lyme disease, approximately 5% of untreated patients may experience acute cardiac involvement. Manifestations of this may include: fluctuating degrees of atrioventricular block, occasionally acute myopericarditis or mild left ventricular dysfunction and, rarely, cardiomegaly or fatal pancarditis (Steere, 2001).

Joint Involvement

Within months after the onset of illness, approximately 60% of untreated patients may have joint involvement. More recent series have reported the frequency of this condition to be \leq 10%, likely due to improved recognition and earlier treatment of patients with early Lyme disease (Wormser, et al., 2006). This condition may be manifested by intermittent attacks of joint swelling and pain, primarily in large joints, especially the knee (Steere, 2001). Knee arthritis may persist for months or even several years in some patients.

Post-Lyme Syndrome

Even after appropriate treatment for Lyme disease, a small number of patients will continue to report subjective complaints. These symptoms, which may last for years, include: primarily musculoskeletal pain, neurocognitive difficulties, or fatigue (Steere, 2001). This syndrome is referred to as chronic Lyme disease, post-Lyme disease syndrome, or post-Lyme syndrome. Authors of a large study reported that the frequency of pain symptoms and fatigue was no greater in patients who had had Lyme disease than in age-matched controls who had not had this infection (Seltzer, et al., 2000). In this study, 678 patients were evaluated in a longitudinal cohort study and a matched cohort study. The researchers reported that “the frequencies of reports of both increased symptoms and increased difficulties with typical activities among patients who had been diagnosed as having Lyme disease were similar to those among age-matched controls without Lyme disease” (Seltzer, et al., 2000).

In the Infectious Disease Society of America (IDSA) clinical practice guidelines, it is noted that there is no well-accepted definition of post-Lyme disease syndrome. In order to provide a framework for future research for this condition and to decrease diagnostic ambiguity, the IDSA guidelines include a proposed definition for this condition (Wormser, et al., 2006). The inclusion criteria for this diagnosis contain the following:

- an adult or child with a documented episode of early or late Lyme disease fulfilling the case definition of the CDC—if based on erythema migrans, the diagnosis must be made and documented by an experienced health care practitioner.
- after treatment of the episode of Lyme disease with a generally accepted treatment regimen, there is resolution or stabilization of the objective manifestation(s) of Lyme disease
- onset of any of the following subjective symptoms within six months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a six-month period after completion of antibiotic therapy:
 - fatigue
 - widespread musculoskeletal pain
 - complaints of cognitive difficulties
 - subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social, or personal activities

The exclusion criteria for the diagnosis include the following:

- an active, untreated, well-documented coinfection (e.g., babesiosis)
- the presence of objective abnormalities on physical examination or on neuropsychologic testing that may explain the patient's complaints (e.g., a patient with antibiotic refractory Lyme arthritis would be excluded; a patient with late neuroborreliosis associated with encephalopathy, who has recurrent or refractory objective cognitive dysfunction, would be excluded.)
- a diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease
- a prolonged history of undiagnosed or unexplained somatic complaints, such as musculoskeletal pains or fatigue, before the onset of Lyme disease
- a diagnosis of an underlying disease or condition that might explain the patient's symptoms
- laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from post-Lyme disease syndrome (e.g., highly elevated erythrocyte sedimentation rate (150 mm/h); abnormal thyroid function; a hematologic abnormality; abnormal levels of serum albumin, total protein, globulin, calcium, phosphorus, glucose, urea nitrogen, electrolytes, or creatinine; significant abnormalities on urine analysis; elevated liver enzyme levels; or a test result suggestive of the presence of a collagen vascular disease)
- although testing by either culture or polymerase chain reaction (PCR), for evidence of *Borrelia burgdorferi* infection is not required, should such testing be done by reliable methods, a positive result would be an exclusion

Lyme Disease Testing

The presence of erythema migrans is considered to be the only manifestation of Lyme disease that is sufficiently distinctive to allow clinical diagnosis in the absence of laboratory confirmation. In a patient with erythema migrans and with compatible epidemiologic and clinical history, the preferred means of diagnosis is a visual inspection of the skin lesion. Serologic testing is considered to be too insensitive in the acute phase, the first two weeks, to be useful for diagnostic purposes. It is appropriate to treat patients on the basis of clinical findings. When there is diagnostic uncertainty, both in the acute and two weeks after the acute phase, serum samples may be tested using the two-step process recommended by the CDC (Wormser, et al., 2006). When testing is indicated, the CDC (1995) recommends a two-step process that includes the following:

- Initial testing should be done with either an enzyme-linked immunosorbent assay (ELISA) or an indirect fluorescent antibody (IFA).
 - When the results of the ELISA or IFA are either equivocal or positive, they should be followed by testing with the more specific Western immunoblot test to corroborate the findings obtained in the first test.
 - When results of ELISA or IFA are negative, there is no need to test further.
- The second step of testing is the Western immunoblot test.
 - If the immunoblot is performed within the first four weeks after the onset of symptoms, both immunoglobulin M (IgM) and immunoglobulin G (IgG) testing should be performed.

- Specific IgM antibodies may not develop for four weeks following the bite of an infected tick, and IgG antibodies may not develop for 6–8 weeks following exposure.
- An IgM immunoblot is considered positive if two of the following three bands are present:
 - 24kDa (OspC)
 - 39 kDa (BmpA)
 - 41 kDa (Fla).
- An IgG immunoblot is considered positive if five of the following 10 bands are present:
 - 18 kDa
 - 21 kDa (OspC)
 - 28 kDa
 - 30 kDa
 - 39 kDa (BmpA)
 - 41 kDa (Fla)
 - 45 kDa
 - 58 kDa (not GroEL)
 - 66 kDa
 - 93 kDa.

Klempner et al. (2001a) reported findings regarding the reliability of two Lyme disease tests: an IgG Western blot blood test and Lyme urine antigen test, or LUAT. The LUAT is not approved by the FDA as a valid diagnostic test for Lyme disease, although it is widely used (NIAID, 2001). The study included 21 patients with a history of acute Lyme disease, as defined by the CDC, who had chronic (six-month duration) fatigue, musculoskeletal pain, or neurocognitive impairment despite treatment with recommended antibiotics. Ten healthy control subjects were included. Serum samples were obtained from all subjects, along with urine samples from the 10 control subjects. The initial Western blot analysis was negative in all 10 control subjects. In the 21 patients with Lyme disease, the results of the initial Western blot analysis were positive in 14 cases and negative in seven. Analysis of duplicate specimens yielded identical results in all 21 patients. The LUAT results varied widely. At least one urine fraction from each of the 10 samples examined tested false-positive. Two urine samples consistently showed false-positive results. Replicates of the eight remaining samples examined were a mixture of positive and negative values; therefore, it was not possible to conclude if they were positive or negative. The authors concluded that the urine test should not be used for the laboratory diagnosis of active or suspected Lyme disease.

In 2005, the CDC published a caution regarding testing for Lyme disease (CDC, 2005). It was noted that the “CDC and the Food and Drug Administration (FDA) have become aware of commercial laboratories that conduct testing for Lyme disease by using assays whose accuracy and clinical usefulness have not been adequately established. These tests include urine antigen tests, immunofluorescent staining for cell wall-deficient forms of *Borrelia burgdorferi* and lymphocyte transformation tests. In addition, some laboratories perform polymerase chain reaction tests for *B. burgdorferi* DNA on inappropriate specimens such as blood and urine or interpret Western blots using criteria that have not been validated and published in peer-reviewed scientific literature” (CDC, 2005). The CDC restated their previous recommendations for testing. Included also was a reminder that diagnosis of Lyme disease should be made after evaluation of a patient’s clinical presentation and risk for exposure to infected ticks and, if indicated, after the use of validated laboratory tests.

Lyme Disease Treatment

In 2006, the Infectious Disease Society of America (IDSA) published updated evidence-based practice guidelines for the treatment of Lyme disease (Wormser, et al., 2006). The revised guidelines contain recommendations for treating a patient with a tick bite with a single dose of doxycycline (200 mg dose) when all of the following circumstances are present (Wormser, et al., 2006):

- the attached tick can be reliably identified as an adult or nymphal *I. scapularis* tick that is estimated to have been attached for ≥ 36 hours on the basis of the degree of engorgement of the tick with blood or of certainty about the time of exposure to the tick
- prophylaxis can be started within 72 hours of the time that the tick was removed
- ecologic information indicates that the local rate of infection of these ticks with *B. burgdorferi* is $\geq 20\%$
- doxycycline treatment is not contraindicated

The time limit of 72 hours is recommended because of the absence of data on the efficacy of chemoprophylaxis for tick bites following tick removal after longer time intervals. The infection rate of ticks with *B. burgdorferi* of $\geq 20\%$ is noted to generally occur in parts of New England, in parts of the Mid-Atlantic states, and in parts of Minnesota and Wisconsin, but not in most other locations in the United States. Patients who have removed attached ticks from themselves, including those who have received antibiotic prophylaxis, should be observed closely for signs and symptoms of tick-borne diseases for up to 30 days. The guidelines recommend that health care practitioners, in endemic areas in particular, should learn to identify the *I. scapularis* ticks, including the various stages and to differentiate ticks that are partially engorged with blood. The testing of ticks for tick-borne infectious agents is not recommended, except in research studies (Wormser, et al., 2006).

The guidelines note that some practitioners prescribe a ten–14 day course of prophylactic amoxicillin for pregnant woman after an *Ixodes scapularis* tick bite. This is based on case reports that indicate Lyme disease during pregnancy may be associated with adverse outcomes for the fetus. However, the guidelines note that there is also some evidence from clinical and epidemiologic studies that suggest favorable outcomes can be expected when pregnant women with Lyme disease are treated with standard antibiotic regimens (Wormser, et al., 2006).

The guidelines include the following recommendations for treatment (Wormser, et al., 2006):

- Early Lyme disease:
 - Administration of doxycycline (100 mg twice daily), amoxicillin (500 mg three times daily), or cefuroxime axetil (500 mg orally twice daily) for 14–21 days is recommended for treatment of early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of neurological involvement or third-degree atrioventricular heart block .
 - Doxycycline is relatively contraindicated during pregnancy or lactation and for children less than eight years old.
 - Doxycycline is also efficacious for treatment of HGA, which may occur simultaneously with early Lyme disease.
 - The recommendation for children is: amoxicillin at a dosage of 50 mg/kg/d, divided into three doses per day (maximum 500 mg/dose), or doxycycline (for those over eight years old) at a dosage of 1–2 mg/kg twice per day (maximum, 100 mg/dose). Cefuroxime axetil, at a dosage of 30 mg/kg/d, divided into two doses daily (maximum, 500 mg/dose), is an acceptable alternative agent.
 - Ceftriaxone (2 g intravenous [IV] daily), although effective, is not superior to oral agents and is therefore not recommended for treatment of Lyme disease in the absence of neurological involvement or third-degree atrioventricular heart block.
- Early Lyme disease with acute neurological disease manifested by meningitis or radiculopathy or cardiac disease manifested by third-degree atrioventricular heart block:
 - Ceftriaxone (2 g IV daily for 14–28 days) in early Lyme disease is recommended. Parenteral therapy with penicillin G or cefotaxime may be a satisfactory alternative. For adult patients intolerant of both penicillin and cephalosporins, doxycycline (200–400 mg/d in two divided doses orally [or IV if unable to take oral medications]) for 14–28 days may be used.
 - For children, IV ceftriaxone or cefotaxime is recommended. Penicillin G given IV is an alternative.
- Late disease with arthritis without neurological disease:
 - Oral regimen as described above for early Lyme disease is recommended.
- Late disease with recurrent arthritis after oral regimen:
 - Oral regimen or parenteral regimen of Ceftriaxone (2 g IV daily for 14–28 days) or parenteral therapy with penicillin G or cefotaxime may be a satisfactory alternative. For adult patients intolerant of penicillin and cephalosporins, doxycycline (200–400 mg/d in two divided doses orally [or IV if unable to take oral medications]) for 14–28 days may be used.
 - For children, IV ceftriaxone or cefotaxime is recommended. Penicillin G given IV is an alternative.
- Late disease with persistent arthritis after two courses of antibiotics
 - Symptomatic therapy is recommended.
- Late disease with central nervous system involvement or peripheral nervous system disease:

- Parenteral regimen of Ceftriaxone (2 g IV daily for 14–28 days) or parenteral therapy with penicillin G or cefotaxime may be a satisfactory alternative. For adult patients intolerant of penicillin and cephalosporins, doxycycline (200–400 mg/d in two divided doses orally [or IV if unable to take oral medications]) for 14–28 days may be used.
- For children, IV ceftriaxone or cefotaxime is recommended. Penicillin G given IV is an alternative.
- Post-Lyme disease syndrome
 - Symptomatic therapy is recommended.

Due to their lower efficacy, macrolide antibiotics are generally not considered first-line treatment for early Lyme disease. They may be used when patients are intolerant of, or should not take, amoxicillin, doxycycline, and cefuroxime axetil. Patients who have received macrolide antibiotics should be closely monitored to ensure resolution of the clinical manifestations (Wormser, et al., 2006).

The IDSA guidelines indicate that Lyme arthritis is usually treated successfully with antimicrobial agents administered orally or IV; the oral method is considered easier to administer than the IV antibiotics, is associated with fewer serious complications, and is less expensive. However, there is a disadvantage in that some patients treated with oral agents have subsequently manifested overt neuroborreliosis, which requires treatment with IV antibiotics. For patients with persistent or recurrent joint swelling after the recommended course of antibiotics, it is recommended that they have a repeat treatment with another four-week course of oral antibiotics or a two- to four-week course of IV ceftriaxone. It is recommended, due to the slow resolution of inflammation, that clinicians consider waiting several months before repeating treatment. If the condition persists after two courses of oral therapy or one course of IV therapy, symptomatic treatment is recommended. This treatment may include: nonsteroidal anti-inflammatory agents, intra-articular steroids, or if significant pain or functional limitation is present, arthroscopic synovectomy.

With regard to post-Lyme disease syndrome, the IDSA guidelines note that, “to date, there is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease. Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (i.e., ≥ six months) subjective symptoms after administration of recommended treatment regimens for Lyme disease” (Wormser, et al., 2006). There have been proposals that patients with chronic Lyme disease may require long-term treatment with IV antibiotic treatment. There does not appear to be evidence in the scientific literature to support this. In addition, treatment with IV antibiotics has a significant risk of complications and side effects. These may include ceftriaxone-associated biliary complication, IV catheter-associated bacterial bloodstream infections, or clostridium difficile-associated diarrhea (Patel, et al., 2000). The IDSA guidelines recommend that for post-Lyme disease, consider and evaluate other potential causes of symptoms; then if none are found, administer symptomatic therapy.

The IDSA guidelines include a list of treatments that are not recommended for patients with any manifestation of Lyme disease. Regarding these treatments, the guidelines note that, “there is a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patients.” These treatments include the following (Wormser, et al., 2006):

- first generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G
- combinations of antimicrobials
- pulsed-dosing (i.e., dosing on some days but not others)
- long-term antibiotic therapy
- anti-bartonella therapies
- hyperbaric oxygen,
- ozone
- fever therapy
- intravenous immunoglobulin
- cholestyramine
- intravenous hydrogen peroxide
- specific nutritional supplements

Literature Review

Fallon et al. (2008) conducted a randomized, placebo-controlled trial comparing clinical improvement from 10 weeks of IV ceftriaxone as compared with IV placebo in patients with previously treated Lyme disease who had objective memory impairment and a currently positive IgG Western blot. The study included 37 patients and 20 healthy volunteers. Patients were randomly assigned to ten weeks of double masked treatment with IV ceftriaxone or placebo and then no antibiotic therapy. The primary outcome measurement was neurocognitive performance, specifically memory, at week 12. At week 24 durability of benefit was evaluated. The enrolled patients had mild to moderate cognitive impairment and marked levels of fatigue, pain and impaired physical functioning. Of 37 patients, 30 completed the full 10 week course (17 in antibiotic group; 13 in placebo group). After 12 weeks of treatment generalized cognitive improvement was noted in antibiotic group. This was not specific to domain and was moderate in magnitude. The improvement between baseline and week 12 in antibiotic treated patients was better than in both placebo-treated patients ($p=0.053$) and the healthy controls ($p<0.01$). This improvement was not seen at 24 weeks. On secondary outcome, patients with more severe fatigue pain and impaired physical functioning who received antibiotics were improved at week 12. At 24 weeks these changes were sustained for pain and physical functioning. Adverse events from either the study medication or the IV line were noted among six of 23 (26.1%) of the patients who received ceftriaxone and in one of 14 (7.1%) of patients who received placebo. Limitations of the study included the small sample size and the lack of post-treatment lumbar puncture of neurologic exam.

Wormser et al. (2003) conducted a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of different durations of oral doxycycline treatment and the combination of oral doxycycline and a single IV dose of ceftriaxone. Outcomes were based on clinical observations and neurocognitive testing, assessed at 20 days, three months, 12 months, and 30 months. One hundred and eighty patients, at least 16 years of age and who met the CDC's surveillance definition of Lyme disease were studied. Patients were randomly assigned to one of three treatment groups: single dose of IV ceftriaxone followed by 10 days of oral placebo capsules; a placebo injection followed by 10 days of oral doxycycline and then followed by 10 days of oral placebo daily; or a placebo injection followed by 20 days of oral doxycycline. It was noted that at all time points, the complete response rate was similar for the three treatment groups: the complete response rate at 30 months was 83.9% in the 20-day doxycycline group, 90.3% in the 10 day doxycycline group, and 86.5% in the doxycycline-ceftriaxone group. The authors concluded that "extending treatment with doxycycline from 10 to 20 days or adding one dose of ceftriaxone to the beginning of a 10-day course of doxycycline did not enhance therapeutic efficacy in patients with erythema migrans. Regardless of regimen, objective evidence of treatment failure was extremely rare."

Krupp et al. (2003) conducted a randomized, double-masked, placebo-controlled trial for the purpose of determining whether post-Lyme syndrome (PLS) is antibiotic responsive. The study involved 55 patients with Lyme disease who had persistent severe fatigue of at least six or more months after antibiotic therapy. Patients were randomly assigned to receive 28 days of IV ceftriaxone or a placebo. Outcomes were measured at a six-month visit. Positive outcomes were reported as: 1) an improvement in fatigue, as measured by a change of 0.7 points or more on an 11-item fatigue questionnaire; 2) improvement in cognitive function defined by a change of 25% or more on a test of reaction time; and, 3) a laboratory outcome with an investigational measure of cerebrospinal fluid (CSF) infection, outer surface protein A (OspA). It was noted that patients assigned to the ceftriaxone group showed improvement in disabling fatigue compared to the placebo group and that no beneficial treatment effect was observed for cognitive function or the laboratory measure of persistent infection. The authors concluded that "because fatigue (a nonspecific symptom) was the only outcome that improved and because treatment was associated with adverse events, this study does not support the use of additional antibiotic therapy with parenteral ceftriaxone in post-treatment, persistently fatigued patients with PLS" (Krupp, et al., 2003).

Kaplan et al. (2003) conducted a randomized, double-blind, placebo-controlled study for the purpose of determining whether antibiotic therapy improves cognitive function in patients with post-treatment chronic Lyme disease (PTCLD). The study involved 129 patients with physician-documented history of Lyme disease from three study sites in northeast United States. Seventy-eight patients were seropositive for IgG antibodies against *Borrelia burgdorferi*, and 51 were seronegative. Patients in each group were randomly assigned to receive IV ceftriaxone daily for 30 days followed by oral doxycycline daily for 60 days or matching IV and oral placebos. Assessments were made at 90 and 180 days after treatment, with the outcome measurements of cognitive functioning, pain and role functioning scale of the Medical Outcomes Study (MOS); memory, attention and executive functioning assessed using objective tests; and mood assessed using the Beck Depression Inventory and Minnesota Multiphasic Personality Inventory. The results indicated that there were no significant baseline

differences between seropositive and seronegative groups. The combined groups showed significant decrease in MOS symptoms, higher objective test scores and improved mood; however, it was noted that there were no significant differences between those receiving antibiotics and placebo.

Klempner et al. (2001b) conducted two randomized trials for the purpose of determining the efficacy of treatment with antibiotics in patients with persistent symptoms of Lyme disease. One trial involved 78 patients who were seropositive for IgG antibodies to *Borrelia burgdorferi* at the time of enrollment, and the other study involved 51 patients who were seronegative. The patients were randomly assigned in a 1:1 ratio to receive either the antibiotics or the placebo. The patients received either IV ceftriaxone daily for 30 days, followed by oral doxycycline daily for 60 days, or matching IV and oral placebos. Each patient had persistent symptoms despite previous treatment for Lyme disease. These reported symptoms included musculoskeletal pain, neurocognitive symptoms or dysesthesia, often associated with fatigue. Outcomes were measured with the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) at 180 days. The results indicated that there were no significant differences in outcomes with prolonged antibiotic treatment as compared with placebo among either the seropositive or seronegative groups.

Gerber et al. (1996) conducted a prospective, longitudinal, community-based cohort study of children with newly diagnosed Lyme disease in an area of Connecticut in which the disease is highly endemic, for the purpose of obtaining data regarding clinical manifestations and outcomes in children. All children from five pediatric practices who were given a diagnosis of Lyme disease of recent onset were eligible to be enrolled. Over a period of 20 months, 201 consecutive patients were enrolled. All but three of the 201 patients were treated for 2–4 weeks with conventional antimicrobial therapy. Ninety-six percent of these patients were treated with oral antibiotics. After four weeks, 94% were completely asymptomatic. At follow-up (i.e., a mean of 25.4 months later), none of the patients had evidence of either chronic or recurrent Lyme disease.

Professional Societies/Organizations

The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) published evidenced-based practice parameters for the treatment of nervous system Lyme disease, which are endorsed by the Infectious Disease Society of America (IDSA). Recommendations in the QSS/AAN practice parameters include (Halperin, et al., 2007):

- Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for CNS Lyme disease with or without parenchymal involvement.
- Oral doxycycline is probably a safe and effective treatment for peripheral nervous system Lyme disease and for CNS Lyme disease without parenchymal involvement. Amoxicillin and cefuroxime axetil may provide alternatives, but supporting data are lacking.
- Prolonged courses of antibiotics do not improve the outcome of post-Lyme syndrome, are potentially associated with adverse events, and are therefore not recommended.
- Recommended duration of both oral and parenteral regimens is 14 days, although it is noted that published studies have used courses ranging from 10 to 28 days without significantly different outcomes.

In 2006, the Infectious Disease Society of America (IDSA) published updated evidence-based guidelines for the clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis), and babesiosis (Wormser, et al., 2006). These evidence-based practice guidelines contain recommendations for treatment of Lyme disease with information is provided about prevention, epidemiology, clinical manifestations, diagnosis, and treatment. The guideline include tables with doses and durations of recommended antimicrobial therapy for treatment and prevention of Lyme disease, a partial listing of therapies to be avoided, and a proposed definition of post-Lyme disease syndrome.

In 2008, the IDSA convened a review panel whose task was to determine whether or not the 2006 Lyme Guidelines were based on sound medical/scientific evidence and whether or not these guidelines required change or revision. The review panel held an all-day open public hearing to offer a forum for the presentation of relevant information on the diagnosis and treatment of Lyme disease. A comprehensive literature search and retrieval was conducted by the panel and IDSA staff. A public input period of more than 80 days was held to allow the public to submit information and to ensure that all points of view were taken into consideration. Each review panel member was assigned a section of the 2006 Lyme Guidelines and was assigned the careful review

of the evidence and other information submitted and/or presented relevant to that section—with all review panel members performing a comprehensive review of the section on Post-Lyme Syndromes. In 2010, the review panel published their final report which noted that based on its review of all the evidence and information provided, no changes or revisions to the 2006 Lyme Guidelines are necessary at this time. The review panel found, “that the 2006 Lyme Guidelines were based on the highest-quality medical/scientific evidence available at the time and are supported by evidence that has been published in more recent years. The Review Panel did not find that the authors of the 2006 Lyme Guidelines had failed to consider or cite relevant data and references that would have altered the published recommendations.” (IDSA, 2010).

Summary

Lyme disease is a tick-borne disease that is endemic to several regions of North America. The best method available for prevention of this disease is to avoid tick-infested areas. In general, when Lyme disease is diagnosed early, favorable outcomes are achieved with the use of oral antibiotic treatment. There are situations where a 14- to 28-day course of intravenous (IV) antibiotics may be medically necessary. It has not been demonstrated in the medical literature that continuous or repeat courses of IV antibiotics are medically necessary for treatment of persistent symptoms, late Lyme disease or post-Lyme disease syndrome.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary up to 28 days for intravenous antibiotic therapy for the treatment of Lyme disease as outlined in the Coverage Policy:

CPT[®]* Codes	Description
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96367	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion, up to 1 hour (List separately in addition to code for primary procedure)
96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure)

HCPCS Codes	Description
S9494	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately, per diem) (do not use this code with home infusion codes for hourly dosing schedules S9497-S9504)
S9497	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; once every 3 hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9500	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; once every 24 hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9501	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; once every 12 hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits

	coded separately), per diem
S9502	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; once every 8 hours, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9503	Home infusion therapy, antibiotic, antiviral, or antifungal; once every 6 hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9504	Home infusion therapy, antibiotic, antiviral, or antifungal; once every 4 hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-9-CM Diagnosis Codes	Description
088.81	Lyme Disease
711.80-711.89	Arthropathy associated with other infectious and parasitic diseases

*Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	8/15/2008	0400	Lyme Disease Treatment

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