Medical Coverage Policy

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Lyme Disease Treatment— Antibiotic Treatment

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Coverage Policy

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

Up to 28 days of intravenous antibiotic therapy for the treatment of Lyme disease is considered medically necessary.

The use of ANY of the following treatments for Lyme disease is considered experimental, investigational or unproven for this indication (this list may not be all-inclusive):

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

A continuous treatment lasting longer than 28 days or a repeat course of parenteral antibiotics for the treatment of Lyme disease with a co-infection with babesiosis or human granulocytic anaplasmosis (HGA) is considered experimental, investigational or unproven.

The placement, maintenance or removal of any of the following as well as any associated supply and/or service and supplies used for or in connection with treatments for Lyme disease that are considered experimental, investigational or unproven is considered not medically necessary:

- peripherally inserted central catheter (PICC) line
- peripherally inserted intravenous catheter
- centrally inserted intravenous catheter

Overview

This Coverage Policy addresses the treatment of Lyme disease with parenteral antibiotics.

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.

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.

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, encephalomyelitits. 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).

In the United States, cranial neuropathy is the most common manifestation of early neurologic Lyme disease. Seventh nerve palsy is the most common of the cranial neuropathies, and bilateral involvement may occur. In areas where Lyme disease is endemic, approximately one in four patients who present with seventh nerve palsy in non-winter months may have Lyme disease. Seventh nerve palsy due to Lyme disease may develop in patients who have no recollection of an erythema migrans lesion or of a tick bite (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/Lyme Arthritis
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 ≤ 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).

Lyme arthritis is a monoarticular or oligoarticular form of arthritis that typically involves the knee. There may be involvement of other large joints or the temporomandibular joint. Large knee effusions that are out of proportion to the pain are characteristic. A Baker’s cyst may develop and rupture. Lyme arthritis is frequently intermittent in nature if untreated, with episodes of joint inflammation spontaneously resolving after a few weeks to a few months. Persistent swelling of the same joint for 12 months would be an unusual presenting manifestation of Lyme arthritis (Wormser, et al., 2006).

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 co-infection (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 (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.

The CDC notes that some laboratories offer Lyme disease testing using assays whose accuracy and clinical usefulness have not been adequately established. Unvalidated tests that are available include but are not limited to (CDC 2011):

- Capture assays for antigens in urine
- Culture, immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms of B. burgdorferi
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- "Reverse Western blots"

- In-house criteria for interpretation of immunoblots
- Measurements of antibodies in joint fluid (synovial fluid)
- IgM or IgG tests without a previous ELISA/EIA/IFA

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., 2006/2010). 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:

- 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 ≥ 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 ≥ 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. Individuals 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., 2006/2010).

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., 2006/2010):

- 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., 2006/2010).

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 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., 2006/2010). 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 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., 2006/2010):

- 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

Berende et al. (2016) conducted a randomized, double-blind, placebo-controlled trial to assess whether longer-term antibiotic treatment of persistent symptoms attributed to Lyme disease leads to better outcomes than does shorter-term treatment. Two hundred eighty patients with persistent symptoms attributed to Lyme disease were randomized to receive a 12-week oral course of doxycycline (n=86), clarithromycin plus hydroxychloroquine (n=96), or placebo (n=98). All study groups received open label intravenous ceftriaxone for two weeks before initiating the randomized regimen. The primary outcome measure was health-related quality of life, assessed by the physical-component summary score of the RAND-36 Health Status Inventory (RAND SF-36) (range, 15 to 61, with higher scores indicating better quality of life), at the end of the treatment period at week 14, after the two-week course of ceftriaxone and the 12-week course of the randomized study drug or placebo had been completed. The SF-36 physical component summary score did not differ significantly among the three study groups at the end of the treatment period, with mean scores of 35.0 (95% confidence interval [CI], 33.5 to 36.5) in the doxycycline group, 35.6 (95% CI, 34.2 to 37.1) in the clarithromycin–hydroxychloroquine group, and 34.8 (95% CI, 33.4 to 36.2) in the placebo group (P=0.69; a difference of 0.2 [95% CI, –2.4 to 2.8] in the doxycycline group vs. the placebo group and a difference of 0.9 [95% CI, –1.6 to 3.3] in the clarithromycin–hydroxychloroquine group vs. the placebo group). The score also did not differ significantly among the groups at subsequent study visits (P = 0.35). In all the groups, the SF-36 physical-component summary score increased significantly from baseline to the end of the treatment period (P<0.001). The rates of adverse events were similar among the study groups. Four serious adverse events thought to be related to drug use occurred during the two-week open-label ceftriaxone phase, and no serious drug-related adverse event occurred during the 12-week randomized phase. The authors concluded that in patients with persistent symptoms attributed to Lyme disease, longer-term antibiotic treatment did not have additional beneficial effects on health-related quality of life beyond those with shorter-term treatment.

DeLong et al. (2012) reported on a biostatistical review of four randomized controlled trials (RCT) that evaluated antibiotic retreatment, focusing on trial design, analysis and conclusions. The four studies enrolled different subpopulations of patients with persistent symptoms, but all examined intravenous (IV) ceftriaxone for a minimum of four weeks and evaluated various primary and secondary treatment effects at approximately three to six. The methodology and results of these studies were included in the review: Fallon, et al (2008), Kaplan et al. (2003), Krupp et al. (2003) and Klempner et al. (2001). The authors found design assumptions for the primary outcomes in the two Klempner trials and two outcomes in the Krupp trial were unrealistic and the trials were likely underpowered to detect clinically meaningful treatment effects. Their findings indicated that the Klempner trials were analyzed using inefficient statistical methods. Regarding the Krupp trial, the authors found that the RCT was well-designed and analyzed for fatigue, finding statistically significant and clinically meaningful

improvement and that the Fallon study corroborated this finding. The authors note that “It is incorrect to draw strong conclusions regarding antibiotic retreatment in patients with persistent symptoms of Lyme disease based on the four NIH-sponsored, randomized controlled trials discussed in this review. Inadequacies in trial designs and the small sample sizes leave many questions unanswered, and underscore the need for additional clinical research on this question.” The authors offer no evidence that repeated or long term antibiotics are actually effective in treating symptoms experienced by individuals after completion of currently recommended antibiotic regimen for treatment of Lyme disease. The evidence is insufficient regarding improved health outcomes from long-term antibiotic therapy for the treatment of Lyme disease. Evidence from well-designed, randomized, controlled trials regarding the efficacy of long term antibiotic therapy for treatment of Lyme disease is needed before the therapy is considered effective for treatment of the condition.

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., 2006/2010). 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).

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.

It has not been demonstrated in the medical literature that continuous or repeat courses of IV antibiotics are medically necessary for treatment Lyme disease with a co-infection with babesiosis or human granulocytic anaplasmosis (HGA).

Babesiosis: Infection due to B. microti occurs in parts of New England, New York State, New Jersey, Minnesota, and Wisconsin. Infection has been recognized, in only a limited portion of the geographic areas where Lyme disease is endemic, with the number of reported cases of babesiosis less than that of Lyme disease in these areas (Wormser, et al., 2006/2010).

The clinical features of babesiosis are similar to those of malaria and range in severity from asymptomatic to rapidly fatal. Most patients experience a viral infection–like illness with fever, chills, sweats, myalgia, arthralgia, anorexia, nausea, vomiting, or fatigue. On physical examination, fever, splenomegaly, hepatomegaly, or jaundice may be seen. Laboratory findings may include hemolytic anemia with an elevated reticulocyte count, thrombocytopenia, proteinuria, and elevated levels of liver enzymes, blood urea nitrogen, and creatinine. Complications include acute respiratory failure, disseminated intravascular coagulation, congestive heart failure, coma, and renal failure. Approximately one-quarter of infected adults and one-half of children experience asymptomatic infection or such mild viral–like illness that the infection is only incidentally diagnosed by laboratory testing (Wormser, et al., 2006/2010).

The IDSA guidelines recommend that patients with active babesiosis should be treated with antimicrobials due to the risk of complications. Diagnostic criteria for active babesial infection should include the presence of viral

infection–like symptoms and identification of babesial parasites in blood by smear evaluation or by polymerase chain reaction (PCR) amplification of babesial DNA. Symptomatic patients whose serum contains antibody to babesia but whose blood lacks identifiable babesial parasites on smear or babesial DNA by PCR should not receive treatment. Treatment is also not recommended for asymptomatic individuals, regardless of the results of serologic examination, blood smears, or PCR. Asymptomatic patients with positive babesial smears and/or PCR should have these studies repeated, and a course of treatment should be considered if parasitemia persists for 13 months (Wormser, et al., 2006/2010).

The IDSA guidelines include the following recommendation for treatment of babesiosis (Wormser, et al., 2006/2010):

- All patients with active babesiosis should be treated with antimicrobial therapy because of the risk of complications.
- Diagnostic criteria for active babesial infection should include the presence of viral infection–like symptoms and identification of babesial parasites in blood by smear evaluation or by PCR amplification of babesial DNA.
- Symptomatic patients whose serum contains antibody to Babesia but whose blood lacks identifiable babesial parasites on smear or babesial DNA by PCR should not receive treatment.
- Treatment is also not recommended for asymptomatic individuals regardless of the results of serologic tests, blood smears, or PCR.
- Asymptomatic patients with positive babesial smear and/or PCR results should have these studies repeated, and a course of treatment should be considered if parasitemia persists for over three months.
- Recommended treatment includes:
  - The combination of either atovaquone plus azithromycin or clindamycin plus quinine for seven to ten days is the initial therapy that should be considered for patients with babesiosis.
  - Clindamycin and quinine should be given to those with severe babesiosis. In such patients, clindamycin should be administered intravenously rather than orally, and exchange transfusion should be considered. Longer duration of antimicrobial therapy may be necessary in highly and persistently symptomatic patients until parasitemia is cleared, but no controlled studies exist that define the risk-benefit ratio of more prolonged therapy.
  - The dosage regimen of atovaquone plus azithromycin for adults is atovaquone, 750 mg orally every 12 hours, and azithromycin, 500–1000 mg on day one and 250 mg once per day thereafter by the oral route. For immunocompromised patients with babesiosis, higher doses of azithromycin (600–1000 mg per day) may be used. The doses for children are atovaquone, 20 mg/ kg every 12 hours (up to a maximum of 750 mg per dose), and azithromycin, 10 mg/kg per day once per day on day one (up to a maximum of 500 mg per dose) and 5 mg/kg once per day (up to a maximum of 250 mg per dose) thereafter orally.
  - The dosage regimen of clindamycin plus quinine for adults is clindamycin, 300–600 mg every six hours intravenously or 600 mg every eight hours orally, and quinine, 650 mg every six to eight hours orally. Doses for children are clindamycin, 7–10 mg/kg given every six to eight hours (up to a maximum of 600 mg per dose) intravenously or orally, and quinine, 8 mg/kg given every eight hours (up to a maximum of 650 mg per dose) orally.
  - Partial or complete RBC exchange transfusion is indicated for those with severe babesiosis, as indicated by high-grade parasitemia (≥10%), significant hemolysis, or renal, hepatic, or pulmonary compromise. No data are available to determine whether partial exchange transfusion is preferable to whole blood exchange. An expert consultation with an infectious diseases expert and a hematologist is recommended.
- Patients with moderate-to-severe babesiosis should be monitored closely during therapy to ensure clinical improvement and improvement of parasitemia and other laboratory abnormalities. In patients with mild-to-moderate babesiosis, clinical improvement should occur within 48 hours after antiprotozoal therapy is begun, and symptoms should completely resolve within three months of initiation of therapy. In severely ill patients, the hematocrit and percentage of parasitized erythrocytes should be monitored daily or every other day until the patient has improved and the level of parasitemia has decreased to<5% of erythrocytes. Some patients may have persistence of low-grade parasitemia for months after specific antimicrobial therapy.

- Physicians should consider the possibility of co-infection with B. burgdorferi or A. phagocytophilum or both in patients with especially severe or persistent symptoms, despite appropriate antibabesial therapy. Patients found to have co-infection should be treated with additional antimicrobial therapy, as recommended for early Lyme disease.
- An underlying immunodeficiency (including asplenia or prior splenectomy, malignancy, and HIV infection) also should be considered in patients with severe or prolonged episodes of babesiosis.
- Re-treatment of patients with antibabesial therapy, as outlined above, should be considered if babesial parasites or amplifiable babesial DNA is detected in blood more than months after initial therapy, regardless of symptom status. However, such assays need not be done routinely for immunocompetent patients who are asymptomatic.

Human Granulocytic Anaplasmosis (HGA): HGA is a rickettsial infection of neutrophils. The infectious agent, A phagocytophilum, is transmitted by the bite of infected Ixodes ticks, and human infection occurs in areas in the United States and Europe where Lyme disease is endemic. Compared to Lyme disease, HGA is infrequently diagnosed in children. Clinical manifestations are nonspecific and may include fever, chills, headache, and myalgias. Laboratory findings may include leukopenia, lymphopenia, thrombocytopenia, and mild elevation of liver enzyme levels. Generally, HGA is a mild, self-limited illness, and all clinical signs and symptoms resolve in most patients within 30 days, even without antibiotic therapy. However, serious manifestations of infection, including a fatal outcome, have been reported in patients with factors known to suppress the immunologic response to infection, such as advanced age, immunosuppressive therapy, chronic inflammatory illnesses, or underlying malignant diseases. Chronic infections have not been described in humans (Wormser, et al., 2006).

The IDSA guidelines include the following recommendation for treatment of HGA (Wormser, et al., 2006):

- All symptomatic patients suspected to have HGA should be treated with antimicrobial therapy due to the risk of complications.
- Suspicion for HGA is based on the acute onset of unexplained fever, chills, and headache, often in association with thrombocytopenia, leukopenia, and/or increased liver enzyme levels in patients with exposure to I. scapularis or I. pacificus ticks within the prior three weeks. Confirmation of the diagnosis is based on laboratory testing (see above), but antibiotic therapy should not be delayed in a patient with a suggestive clinical presentation pending the results.
- Doxycycline is recommended as the treatment of choice for patients who are suspected to have symptomatic HGA. The recommended dosage regimen for adults is 100 mg twice per day by mouth (or intravenously for those patients unable to take an oral medication) for ten days. This treatment regimen should be adequate therapy for patients with HGA alone and for patients who are co-infected with B. burgdorferi.
- Although a ten-day treatment course of doxycycline may be offered to all children as well, the panel preferred a modified approach in which severity of illness, age of the child, and the presence or absence of co-infection with B. burgdorferi were each considered to minimize an already low risk of drug toxicity. The suggested dosage of doxycycline for children with HGA is four mg/kg per day in two divided doses (maximum, 100 mg per dose) orally (or intravenously for children unable to take an oral medication). Children at least eight years of age may be treated with a ten-day course of doxycycline.
- For severely ill children less than eight years of age without concomitant Lyme disease, the panel recommended an abbreviated treatment course of four to five days. If the child has concomitant Lyme disease, then amoxicillin (50 mg/kg per day in three divided doses; maximum, 500 mg per dose) or cefuroxime axetil (30 mg/kg per day in two divided doses; maximum, 500 mg per dose) should be initiated at the conclusion of the course of doxycycline to complete a 14-day total course of antibiotic therapy.
- Patients with mild illness due to HGA where doxycycline treatment is not appropriate due to a history of drug allergy, pregnancy, or less than eight years of age, may be treated with rifampin for seven to ten days using a dosage regimen of 300 mg twice per day by mouth for adults and 10 mg/kg twice per day for children (maximum, 300 mg per dose). Rifampin treated patients should be closely observed to ensure resolution of clinical and laboratory abnormalities. Because rifampin is not effective therapy for Lyme disease, co-infected patients should also be treated with amoxicillin or cefuroxime axetil as used for the treatment of erythema migrans. No other antimicrobial can be recommended for the treatment of HGA.

- Persistence of fever for 148 hours after initiation of doxycycline suggests that the diagnosis of HGA is incorrect or, more remotely, that the patient is co-infected with B. microti.
- Treatment is not recommended for asymptomatic individuals who are seropositive for antibodies to A. phagocytophilum.

Use Outside of the US
The European Federation of Neurological Societies (EFNS) published guidelines on the diagnosis and management of European Lyme neuroborreliosis (LNB) (Mygland, et al., 2012). The recommendations for treatment include:

Early LNB with Manifestations Confined to the Peripheral Nervous System (PNS) and Meninges:
- Adult patients with definite or possible early LNB with symptoms confined to the meninges, cranial nerves, nerve roots or peripheral nerves (Bannwarth syndrome) should be offered a single 14-day course of antibiotic treatment.
- Oral doxycycline or intravenous (IV) ceftriaxone or IV penicillin or IV cefotaxime are effective and safe treatments (level B).
- Oral doxycycline (200 mg daily) and IV ceftriaxone (2 g daily) for 14 days are equally effective (level A).
- The advantages of doxycycline are the oral route of administration and the lower costs. Doxycycline is relatively contraindicated during pregnancy or lactation.

Early LNB with Central Nervous System (CNS) Symptoms:
- Adult patients with definite or possible early LNB with CNS manifestations (myelitis, encephalitis, vasculitis) should be treated with IV ceftriaxone (2 g daily) for 14 days (not enough evidence: GPP).

Late LNB:
- Adult patients with definite or possible late LNB with peripheral neuropathy and ACA should be treated with oral doxycycline (200 mg daily) or IV ceftriaxone (2 g daily) for 3 weeks (not enough evidence: GPP).
- Adult patients with definite or possible late LNB with CNS manifestations (myelitis, encephalitis, vasculitis) should be treated with IV ceftriaxone (2 g daily) for 3 weeks (not enough evidence: GPP).

Post-Lyme Disease Syndrome (PLDS): Antibiotic therapy has no impact on PLDS (level A).

Pediatric Neuroborreliosis:
- Pediatric patients with definite or possible early LNB with symptoms confined to the meninges, cranial nerves, nerve roots or peripheral nerves (Bannwarth syndrome) should be offered a single 14-day course of antibiotic treatment.
- Oral doxycycline or IV penicillin or IV ceftriaxone or IV cefotaxime is effective and safe treatments (level B).
- Oral doxycycline (200 mg daily) and IV ceftriaxone (2 g daily) for 14 days are equally effective (level B). The advantages of doxycycline are the oral route of administration and the lower costs. Doxycycline is contraindicated in those age <8 years (in some countries 9 years).
- Pediatric patients with CNS manifestations (myelitis, encephalitis, vasculitis) should be treated with IV ceftriaxone (2 g daily) for 14 days (not enough evidence: GPP).

Rating of Recommendations for a Therapeutic Intervention:
Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.
Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.
Good Practice Points (GPPs): Where there was lack of evidence but consensus was clear the Task Force members have stated their opinion as good practice points.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered medically necessary when criteria in the applicable policy statements listed above are met up to 28 days for intravenous antibiotic therapy for the treatment of Lyme disease:

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 of a new drug/substance, 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	Description

Diagnosis Codes	
082.40-082.49	Ehrlichiosis
088.81	Lyme Disease
088.82	Babesiosis
088.89	Other specified arthropod-borne diseases
088.9	Arthropod-borne disease, unspecified
711.80-711.89	Arthropathy associated with other infectious and parasitic diseases

ICD-10-CM Diagnosis Codes	Description
A69.20-A69.29	Lyme disease
A77.40-A77.49	Ehrlichiosis
B60.0	Babesiosis
B60.8	Other specified protozoal diseases
B64	Unspecified protozoal disease

Considered Experimental/Investigational/Unproven for the treatment of Lyme disease for indications listed as such in this 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 of a new drug/substance, 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)
96369	Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to 1 hour, including pump set-up and establishment of subcutaneous infusion site(s)
96370	Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96371	Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); additional pump set-up with establishment of new subcutaneous infusion site(s) (List separately in addition to code for primary procedure)
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
96373	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intra-arterial
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
96375	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug);

	each additional sequential intravenous push of a new substance/drug (list separately in addition to code for primary procedure)
96376	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility (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**
082.40-082.49	Ehrlichiosis
088.81	Lyme Disease
088.82	Babesiosis
088.89	Other specified arthropod-borne diseases
088.9	Arthropod-borne disease, unspecified
711.80-711.89	Arthropathy associated with other infectious and parasitic diseases

ICD-10-CM Diagnosis Codes	**Description**

A69.20-A69.29	Lyme disease
A77.40-A77.49	Ehrlichiosis
B60.0	Babesiosis
B60.8	Other specified protozoal diseases
B64	Unspecified protozoal disease

Considered Not Medically Necessary when intravenous supplies and services are provided in conjunction with treatment of Lyme disease that is considered experimental, investigational, unproven:

CPT®* Codes	**Description**
36555	Insertion of non-tunneled centrally inserted central venous catheter; younger than 5 years of age
36556	Insertion of non-tunneled centrally inserted central venous catheter; age 5 years or older
36557	Insertion of tunneled centrally inserted central venous catheter, without subcutaneous port or pump; younger than 5 years of age
36558	Insertion of tunneled centrally inserted central venous catheter, without subcutaneous port or pump; age 5 years or older
36568	Insertion of peripherally inserted central venous catheter (PICC), without subcutaneous port or pump; younger than 5 years of age
36569	Insertion of peripherally inserted central venous catheter (PICC), without subcutaneous port or pump; age 5 years or older
36570	Insertion of peripherally inserted central venous access device, with subcutaneous port; younger than 5 years of age
36571	Insertion of peripherally inserted central venous access device. with subcutaneous port; age 5 years or older
36589	Removal of tunneled central venous catheter, without subcutaneous port or pump
36590	Removal of tunneled central venous access device, with subcutaneous port or pump, central or peripheral insertion

HCPCS Codes	**Description**
A4221	Supplies for maintenance of non-insulin drug infusion catheter, per week (list drug separately)
A4300	Implantable access catheter, (eg, venous, arterial, epidural, subarachnoid, or peritoneal, etc) external access
A4305	Disposable drug delivery system, flow rate of 50 ml or greater per hour
A4306	Disposable drug delivery system, flow rate of less than 50 ml per hour
C1751	Catheter, infusion, inserted peripherally, centrally or midline (other than hemodialysis)
S5498	Home infusion therapy, catheter care/maintenance, simple (single lumen), includes administrative services, professional pharmacy services, care coordination and all necessary supplies and equipment, (drugs and nursing visits coded separately), per diem
S5501	Home infusion therapy, catheter care/maintenance, complex (more than one lumen), includes administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

S5517	Home infusion therapy, all supplies necessary for restoration of catheter patency or declotting
S5518	Home infusion therapy, all supplies necessary for catheter repair
S5520	Home infusion therapy, all supplies (including catheter) necessary for a peripherally inserted central venous catheter (PICC) line insertion
S5521	Home infusion therapy, all supplies (including catheter) necessary for a midline catheter insertion
S5522	Home infusion therapy, insertion of peripherally inserted central venous catheter (PICC), nursing services only (no supplies or catheter included)
S5523	Home infusion therapy, insertion of midline venous catheter, nursing services only (no supplies or catheter included)

ICD-9-CM Diagnosis Codes	**Description**
082.40-082.49	Ehrlichiosis
088.81	Lyme Disease
088.82	Babesiosis
088.89	Other specified arthropod-borne diseases
088.9	Arthropod-borne disease, unspecified
711.80-711.89	Arthropathy associated with other infectious and parasitic diseases

ICD-10-CM Diagnosis Codes	**Description**
A69.20-A69.29	Lyme disease
A77.40-A77.49	Ehrlichiosis
B60.0	Babesiosis
B60.8	Other specified protozoal diseases
B64	Unspecified protozoal disease

References

1. American Academy of Pediatrics (AAP). Committee on Infectious Diseases. Prevention of Lyme disease. Pediatrics. 2000 Jan;105(1 Pt 1):142-7.

2. Auwaerter PG. Point: antibiotic therapy is not the answer for patients with persisting symptoms attributable to lyme disease. Clin Infect Dis. 2007 Jul 15;45(2):143-8.

3. Bacon RM, Kugeler KJ, Mead PS; Centers for Disease Control and Prevention (CDC). Surveillance for Lyme disease--United States, 1992-2006. MMWR Surveill Summ. 2008 Oct 3;57(10):1-9.

4. Berende A, ter Hofstede HJ, Vos FJ, van Middendorp H, Vogelaar ML, Tromp M, et al. Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease. N Engl J Med. 2016 Mar 31;374(13):1209-20.

5. Borg R, Dotevall L, Hagberg L, Maraspin V, Lotric-Furlan S, Cimperman J, Strle F. Intravenous ceftriaxone compared with oral doxycycline for the treatment of Lyme neuroborreliosis. Scand J Infect Dis. 2005;37(6-7):449-54.

6. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: a position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38.

7. Brouqui P, Bacellar F, Baranton G, Birtles RJ, Bjoersdorff A, Blanco JR, et al. European Network for Surveillance of Tick-Borne Diseases. Guidelines for the diagnosis of tick-borne bacterial diseases in Europe. Clin Microbiol Infect. 2004 Dec;10(12):1108-32.

8. Cameron D, Gaito A, Harris N, Bach G, Bellovin S, Bock K; ILADS Working Group. Evidence-based guidelines for the management of Lyme disease. Expert Rev Anti Infect Ther. 2004;2(1 Suppl):S1-13.

9. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35.

10. Centers for Disease Control and Prevention (CDC). Division of Vector-Borne Infectious Diseases. Lyme Disease. Page last reviewed: Page last reviewed: March 4, 2015; Page last updated: May 23, 2017. Accessed June 2, 2017. Available at URL address: http://www.cdc.gov/lyme/

11. Centers for Disease Control and Prevention (CDC). Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep. 1995 Aug 11;44(31):590-1. Accessed June 2, 2017. Available at URL address: http://www.cdc.gov/mmwr/preview/mmwrhtml/00038469.htm

12. Centers for Disease Control and Prevention (CDC). Case definitions for infectious conditions under public health surveillance. MMWR Recomm Rep. 1997 May 2;46(RR-10):1-55. Accessed June 2, 2017. Available at URL address: http://www.cdc.gov/mmwr/preview/mmwrhtml/00047449.htm

13. Centers for Disease Control and Prevention (CDC). Notice to readers: caution regarding testing for Lyme disease. MMWR Morb Mortal Wkly Rep. 2005 Feb 11; 54(05);125. Accessed June 2, 2017. Available at URL address: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5405a6.htm

14. Centers for Disease Control and Prevention (CDC). Lyme Disease Data. Page last reviewed: March 20, 2012; Page last updated: Page last reviewed: December 19, 2016; Page last updated: December 19, 2016. Accessed June 2, 2017. Available at URL address: http://www.cdc.gov/lyme/stats/index.html

15. Centers for Disease Control and Prevention (CDC). Lyme Disease Diagnosis and Testing. Other Types of Laboratory Testing. Page last reviewed: March 4, 2015; Page last updated: November 19, 2015. Accessed June 2, 2017. Available at URL address: http://www.cdc.gov/lyme/diagnosistesting/LabTest/OtherLab/index.html

16. Cerar D, Cerar T, Ruzić-Sabljić E, Wormser GP, Strle F. Subjective symptoms after treatment of early Lyme disease. Am J Med. 2010 Jan;123(1):79-86.

17. Delong AK, Blossom B, Maloney EL, Phillips SE. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: a biostatistical review of randomized, placebo-controlled, clinical trials. Contemp Clin Trials. 2012 Nov;33(6):1132-42.

18. Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2008 Mar 25;70(13):992-1003.

19. Feder HM Jr, Abeles M, Bernstein M, Whitaker-Worth D, Grant-Kels JM. Diagnosis, treatment, and prognosis of erythema migrans and Lyme arthritis. Clin Dermatol. 2006 Nov-Dec;24(6):509-20.

20. Feder HM Jr. Lyme disease in children. Infect Dis Clin North Am. 2008 Jun;22(2):315-26.

21. Feder HM Jr, Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP; Ad Hoc International Lyme Disease Group. A critical appraisal of "chronic Lyme disease". N Engl J Med. 2007 Oct 4;357(14):1422-30.

22. Fish AE, Pride YB, Pinto DS. Lyme carditis. Infect Dis Clin North Am. 2008 Jun;22(2):275-88.

23. Gerber MA, Zemel LS, Shapiro ED. Lyme arthritis in children: clinical epidemiology and long-term outcomes. Pediatrics. 1998 Oct;102(4 Pt 1):905-8.

24. Gerber MA, Shapiro ED, Burke GS, Parcells VJ, Bell GL. Lyme disease in children in southeastern Connecticut. Pediatric Lyme Disease Study Group. N Engl J Med. 1996 Oct 24;335(17):1270-4.

25. Halperin JJ, Shapiro ED, Logigian E, Belman AL, Dotevall L, Wormser GP, et al.; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2007 Jul 3;69(1):91-102.

26. Halperin JJ. Nervous system lyme disease. Infect Dis Clin North Am. 2008 Jun;22(2):261-74.

27. Hengge UR, Tannapfel A, Tyring SK, Erbel R, Arendt G, Ruzicka T. Lyme borreliosis. Lancet Infect Dis. 2003 Aug;3(8):489-500.

28. Hoppa E, Bachur R. Lyme disease update. Curr Opin Pediatr. 2007 Jun;19(3):275-80.

29. Hu L. Treatment of Lyme disease. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on June 24, 2016)

30. Infectious Diseases Society of America (IDSA). Final Report of the Lyme Disease Review Panel of the Infectious Diseases Society of America (IDSA). Apr 22, 2010. Accessed: June 2, 2017. Available at URL address: http://www.idsociety.org/Lyme/

31. Kaplan RF, Trevino RP, Johnson GM, Levy L, Dornbush R, Hu LT, et al. Cognitive function in post-treatment Lyme disease: do additional antibiotics help? Neurology. 2003 Jun 24;60(12):1916-22.

32. Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, et al. (a)Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001 Jul 12;345(2):85-92.

33. Klempner MS, Schmid CH, Hu L, Steere AC, Johnson G, McCloud B et al. (b). Intralaboratory reliability of serologic and urine testing for Lyme disease. Am J Med. 2001 Feb 15;110(3):217-9.

34. Klempner MS, Baker PJ, Shapiro ED, Marques A, Dattwyler RJ, Halperin JJ, Wormser GP. Treatment Trials for Post-Lyme Disease Symptoms Revisited. Am J Med. 2013 Jun 10. doi:pii: S0002-9343(13)00201-5. 10.1016/j.amjmed.2013.02.014. [Epub ahead of print]

35. Kowalski TJ, Tata S, Berth W, Mathiason MA, Agger WA. Antibiotic treatment duration and long-term outcomes of patients with early lyme disease from a lyme disease-hyperendemic area. Clin Infect Dis. 2010 Feb 15;50(4):512-20.

36. Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30.

37. Lantos PM. Chronic Lyme disease: the controversies and the science. Expert Rev Anti Infect Ther. 2011 Jul;9(7):787-97.

38. Marques A. Chronic lyme disease: a review. Infect Dis Clin North Am. 2008 Jun;22(2):341-60.

39. Mygland A, Ljøstad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I; European Federation of Neurological Societies. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol. 2010 Jan;17(1):8-16, e1-4.

40. Nadelman RB, Nowakowski J, Fish D, Falco RC, Freeman K, McKenna D, et al; Tick Bite Study Group. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. N Engl J Med. 2001 Jul 12;345(2):79-84.

41. National Institute of Allergy and Infectious Diseases (NIAID). National Institutes of Health (NIH). Lyme Disease. Accessed June 2, 2017. Available at URL address: https://www.niaid.nih.gov/diseases-conditions/lyme-disease

42. Oksi J, Nikoskelainen J, Hiekkanen H, Lauhio A, Peltomaa M, Pitkäranta A, Nyman D, et al. Duration of antibiotic treatment in disseminated Lyme borreliosis: a double-blind, randomized, placebo-controlled, multicenter clinical study. Eur J Clin Microbiol Infect Dis. 2007 Aug;26(8):571-81.

43. Pachner AR, Steiner I. Lyme neuroborreliosis: infection, immunity, and inflammation. Lancet Neurol. 2007 Jun;6(6):544-52.

44. Patel R, Grogg KL, Edwards WD, Wright AJ, Schwenk NM. Death from inappropriate therapy for Lyme disease. Clin Infect Dis. 2000 Oct;31(4):1107-9.

45. Pfister HW, Rupprecht TA. Clinical aspects of neuroborreliosis and post-Lyme disease syndrome in adult patients. Int J Med Microbiol. 2006 May;296 Suppl 40:11-6.

46. Puius YA, Kalish RA. Lyme arthritis: pathogenesis, clinical presentation, and management. Infect Dis Clin North Am. 2008 Jun;22(2):289-300.

47. Sanchez E, Vannier E, Wormser GP, Hu LT. Diagnosis, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: A Review. JAMA. 2016 Apr 26;315(16):1767-77.

48. Sapi E, Pabbati N, Datar A, Davies EM, Rattelle A, Kuo BA. Improved culture conditions for the growth and detection of Borrelia from human serum. Int J Med Sci. 2013;10(4):362-76. doi: 10.7150/ijms.5698. Epub 2013 Feb 18.

49. Seltzer EG, Gerber MA, Cartter ML, Freudigman K, Shapiro ED. Long-term outcomes of persons with Lyme disease. JAMA. 2000 Feb 2;283(5):609-16.

50. Shapiro ED. Clinical practice. Lyme disease. N Engl J Med. 2014 May 1;370(18):1724-31.

51. Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2012 Feb 4;379(9814):461-73. Epub 2011 Sep 6.

52. Steere AC, Coburn J, Glickstein L. The emergence of Lyme disease. J Clin Invest. 2004 Apr;113(8):1093-101.

53. Steere AC, Sikand VK, Schoen RT, Nowakowski J. Asymptomatic infection with Borrelia burgdorferi. Clin Infect Dis. 2003 Aug 15;37(4):528-32. Epub 2003 Jul 30.

54. Steere AC, Dhar A, Hernandez J, Fischer PA, Sikand VK, Schoen RT, et al. Systemic symptoms without erythema migrans as the presenting picture of early Lyme disease. Am J Med. 2003 Jan;114(1):58-62.

55. Steere AC. Lyme disease. N Engl J Med. 2001 Jul 12;345(2):115-25.

56. Stricker RB. Counterpoint: long-term antibiotic therapy improves persistent symptoms associated with lyme disease. Clin Infect Dis. 2007 Jul 15;45(2):149-57.

57. Stricker RB, Delong AK, Green CL, Savely VR, Chamallas SN, Johnson L. Benefit of intravenous antibiotic therapy in patients referred for treatment of neurologic Lyme disease. Int J Gen Med. 2011;4:639-46. Epub 2011 Sep 6.

58. Vannier E, Krause PJ. Human babesiosis. N Engl J Med. 2012 Jun 21;366(25):2397-407.

59. Vannier E, Krause PJ. Update on babesiosis. Interdiscip Perspect Infect Dis. 2009;2009:984568.

60. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006 Nov 1;43(9):1089-134 (reaffirmed 2010).

61. Wormser GP. Clinical practice. Early Lyme disease. N Engl J Med. 2006 Jun 29;354(26):2794-801.

62. Wormser GP, Ramanathan R, Nowakowski J, McKenna D, Holmgren D, Visintainer P, et al. Duration of antibiotic therapy for early Lyme disease. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2003 May 6;138(9):697-704.