Medical Coverage Policy

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Lyme Disease Treatment - Antibiotic Treatment

Table of Contents

Related Coverage Resources

Complementary and Alternative Medicine
Hyperbaric and Topical Oxygen Therapies

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers

must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

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

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 not medically necessary 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 not medically necessary.

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 not medically necessary are considered not medically necessary:

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

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing,

transportation and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

Individuals with persistent or chronic Lyme disease (PLD/CLD) often encounter many barriers to care, including insurance coverage, healthcare costs, travel time and distance to obtain care, and availability of care. Individuals report diagnostic delays, having to see many doctors before being diagnosed, traveling significant distances to receive care, and incurring greater out-of-pocket healthcare costs. More than three-quarters (78%) of these patients were not diagnosed within the first 6 months of illness. Most patients see more than four physicians before they are diagnosed, creating delays that may profoundly impact their quality of life. To obtain care, 49% travel more than 50 miles; 31% report traveling 100 miles or more for care. The cost, inconvenience, and work-related impact of traveling these distances may result in many patients foregoing care all together (Johnson and Maloney, 2022).

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 two millimeters in size, 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 (Rosenberg, et al., 2018; Bacon, et al., 2008). Cases are most common in the Northeast, mid-Atlantic, and upper-Midwest regions of the United States (Centers for Disease Control and Prevention [CDC], 2024).

There are several approaches to Lyme disease prevention (CDC, 2024). 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 general, there are three stages or phases of Lyme disease: early localized disease, early disseminated disease, and persistent or late disease (Hu, 2024; Oliveira and Shapiro, 2024; Hengge, et al., 2003). The clinical features of each stage can overlap and some patients present in a later stage of Lyme disease without a history of prior signs or symptoms suggestive of earlier Lyme disease. Early localized disease may be followed within days or weeks by early disseminated disease that affects the nervous system, heart, or joints. Late disease may develop months to a few years after the initial infection. Arthritis may be the presenting manifestation of the disease (Hu, 2024).

The diagnosis of Lyme disease should consider 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, may be falsely negative in patients with erythema migrans.

Early localized disease can occur a few days to one month after a tick bite. According to the CDC (2024), signs and symptoms include fever, chills, headache, fatigue, muscle and joint aches, and swollen lymph nodes may occur in the absence of rash. Additional symptoms may include malaise, lethargy, mild headache, and mild neck stiffness (Hu, 2023). Erythema migrans (EM) rash occurs in approximately 70 to 80 percent of infected people. 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 (average is about seven days). The patch may gradually grow larger reaching up to 12 inches (30 cm) or more across. The rash can appear on any area of the body. 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 one to two weeks 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 weeks to months after a tick bite and can occur in the absence of any prior features of Lyme disease (Hu, 2023). According to the CDC (2024), signs and symptoms include severe headaches and neck stiffness, additional erythema migrans rashes on other areas of the body, facial palsy, arthritis with severe joint pain and swelling, intermittent pain in tendons, muscles, joints and bones, heart palpitations or an irregular heartbeat, episodes of dizziness or shortness of breath, inflammation of the brain and spinal cord, nerve pain, and shooting pains, numbness, or tingling in the hands and feet.
Clinical manifestations include (Hu, 2023):

- carditis including AV nodal block, mild cardiomyopathy or myopericarditis
- neurologic disease including lymphocytic meningitis, cranial neuropathy (most often facial, can be bilateral), peripheral neuropathy, rarely myelitis or encephalitis
- musculoskeletal involvement including migratory arthralgias
- skin involvement - multiple erythema migrans lesions
- lymphadenopathy - regional or generalized
- eye involvement - conjunctivitis, iritis, choroiditis, vitritis, retinitis
- liver disease - liver function test abnormalities, hepatitis
- kidney disease - microhematuria, asymptomatic proteinuria

Late disease, occurring months to years after the tick bite, can occur in the absence of any prior features of Lyme disease (Hu, 2023). Clinical manifestations include (Hu, 2023):

- Musculoskeletal symptoms - approximately 60 percent of untreated patients develop intermittent monoarticular or oligoarticular arthritis; approximately 10 percent of untreated patients develop persistent monoarthritis, usually affecting the knee
- Neurologic disease including peripheral neuropathy or encephalomyelitis
- Cutaneous involvement - acrodermatitis chronica atrophicans, morphea/localized scleroderma-like lesions (both described only in Europe)

Neurological Involvement
Neurologic features of early disseminated Lyme disease may include lymphocytic meningitis, unilateral or bilateral cranial nerve palsies (especially of the facial nerve), radiculopathy (Bannwarth syndrome), peripheral neuropathy, mononeuropathy multiplex, cerebellar ataxia (rarely), and encephalomyelitis (rarely) (Hu, 2024).

The IDSA (Larson, et al., 2021) recommends testing individuals for Lyme disease with the following acute neurologic disorders: meningitis, painful radiculoneuritis, mononeuropathy

multiplex including confluent mononeuropathy multiplex, acute cranial neuropathies (particularly VII, VIII, less commonly III, V, VI, and others), or in patients with evidence of spinal cord (or rarely brain) inflammation, the former particularly in association with painful radiculitis involving related spinal cord segments, and with epidemiologically plausible exposure to ticks infected with B burgdorferi. Lyme disease is one of the few causes of bilateral cranial nerve palsies (Hu, 2024).

Cardiac Involvement
Approximately 1% of untreated patients may experience acute cardiac involvement. Symptoms of cardiac involvement include lightheadedness, syncope, shortness of breath, palpitations, and/or chest pain. The cardiac features of early disseminated Lyme disease typically occur one to two months (range <1 to 28 weeks) after the onset of infection. Manifestations of this may include fluctuating degrees of atrioventricular block, acute myopericarditis mild cardiomyopathy or endocarditis (Hu, 2024).

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 ≤ 30%, likely due to improved recognition and earlier treatment of patients with early Lyme disease (Lantos, et al., 2021). During early disseminated infection, patients may experience migratory pain in joints, bursae, tendons, muscle, or bone in one or a few locations at a time. Some patients develop only migratory arthralgias without arthritis. Arthralgia symptoms may be intermittent or migratory (Schoen, 2024).

Lyme arthritis occurs as a late manifestation of Lyme disease and may begin in any season, weeks to months after initial infection. Lyme arthritis is characterized by intermittent or persistent monoarticular or oligoarticular arthritis that typically involves the knee. There may be involvement of other large joints or the temporomandibular joint. Marked swelling of one or a few large joints that are out of proportion to the pain are characteristic. A popliteal cyst may develop and rupture causing a pseudo-thrombophlebitis of the calf. Lyme arthritis is frequently intermittent in nature if untreated, with episodes of joint inflammation spontaneously resolving after a few weeks to a few months (Schoen, 2024; Lantos, et al., 2021; Wormser, et al., 2006).

In young children, Lyme arthritis may mimic septic arthritis, presenting with fever and a painful, swollen joint, especially with hip involvement. In the following instances, there is considerable overlap between Lyme arthritis and septic arthritis in children: presence of fever, elevated acute phase reactants, and the inability to bear weight (especially when the hip is involved) (Lantos, et al., 2021).

Cutaneous Manifestations of Eurasian Lyme Disease
Borrelial lymphocytoma (BL) and acrodermatitis chronica atrophicans are cutaneous manifestations of Lyme disease that have been primarily observed in European patients with B. afzelii infection. Consequently, patients evaluated in the United States for these conditions will most often have acquired their infection in Europe or in Lyme disease-endemic areas of Central or East Asia. Borrelial lymphocytoma is an inflammatory skin lesion, usually a bluish-purplish nodule, papule, or plaque, which occurs weeks to months after initial infection. Acrodermatitis chronica atrophicans is an atrophic dermatitis affecting extensor surfaces, especially of the hands, and may present months to years after initial infection (Lantos, et al., 2021).

Chronic Lyme Disease
The term chronic Lyme disease has been largely replaced by term "late manifestations" as these syndromes often appear after a long period of apparent clinical latency (Lantos, et al., 2021). The term "chronic Lyme disease" as currently used lacks an accepted definition for either clinical use or scientific study. According to the Infectious Diseases Society of America (IDSA) guidelines for

the prevention, diagnosis and treatment of Lyme disease, in practice, the term has been applied to a highly heterogeneous patient population, including patients with prolonged and unexplained symptoms that lack objective features of Lyme disease and many that prove to have alternative medical diagnoses. However, regardless of the underlying diagnosis, many patients who receive the diagnosis are ill, highly symptomatic and may be quite disabled by the underlying illnesses and symptoms. In the evaluation of these patients, there should be a thorough and individualized history, physical examination and appropriate laboratory investigation to identify, whenever possible, the best-fitting diagnosis. If an alternative diagnosis is established or suspected, further evaluation, treatment and referral should be directed toward that diagnosis. Per the ISDA, there are no high-quality studies regarding the treatment of patients with highly heterogeneous symptoms but no alternative diagnoses. These patients often have no compelling clinical or laboratory support for the diagnosis of ongoing or antecedent Lyme disease. Per the guidelines, prolonged antibiotic treatment is unlikely to benefit individuals who lack a verifiable history of Lyme disease while exposing them to significant risk (Lantos, et al., 2021).

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 (Lantos, et al., 2021; Wormser, et al., 2006). When testing is indicated, the CDC (2024) recommends a two-step process that includes the following (Lantos, et al., 2021):

- 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 six to eight 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 ten 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 (LUAT). The LUAT is not approved by the FDA as a valid diagnostic test for Lyme disease. 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 ten control subjects. The initial Western blot analysis was negative in all ten 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 ten 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. 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. 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, 2023):

- Capture assays for antigens in urine
- 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"
- IgM or IgG tests without a previous ELISA/EIA/IFA

Lyme Disease Treatment
The updated 2020 clinical practice guidelines from the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR) for the prevention, diagnosis, and treatment of Lyme disease include the following recommendations for intravenous antibiotics (Lantos, et al., 2021):

- In patients with Lyme disease-associated meningitis, cranial neuropathy, radiculoneuropathy or with other peripheral nervous system (PNS) manifestations, recommended treatment includes: intravenous (IV) ceftriaxone, cefotaxime, penicillin G, or oral doxycycline over other antimicrobials (strong recommendation, moderate-quality evidence).
  - Comment: Decisions about the choice of antibiotic among these, including the route of administration, should primarily be made based on individual factors such as side effect

profile, ease of administration, ability to tolerate oral medication, concerns about compliance unrelated to effectiveness. Treatment route may be changed from IV to oral during treatment. The preferred antibiotic duration is 14–21 days.

- In patients with Lyme disease-associated parenchymal involvement of the brain or spinal cord, recommend using IV over oral antibiotics (strong recommendation, moderate-quality evidence).

- In the hospitalized patient with Lyme carditis, suggest initial use of IV ceftriaxone over oral antibiotics until there is evidence of clinical improvement, then switching to oral antibiotics to complete treatment (weak recommendation, very low-quality evidence).

- In patients with Lyme arthritis with no or minimal response (moderate to severe joint swelling with minimal reduction of the joint effusion) to an initial course of oral antibiotic, suggest a two- to four-week course of IV ceftriaxone over a second course of oral antibiotics (weak recommendation, low-quality evidence).

- In patients who have failed one course of oral antibiotics and one course of IV antibiotics, suggest a referral to a rheumatologist or other trained specialist for consideration of the use of disease modifying anti-rheumatic drugs (DMARDs), biologic agents, intraarticular steroids, or arthroscopic synovectomy (weak recommendation, very low-quality evidence).
  - Comment: Antibiotic therapy for longer than eight weeks is not expected to provide additional benefit to patients with persistent arthritis if that treatment has included one course of IV therapy.

Several antibiotics and antibiotic classes are not indicated to treat Lyme disease due to a variety of considerations, including lack of in vitro activity, the absence of supportive clinical data, potential toxicity, and an unnecessarily broad spectrum of antimicrobial activity. The following drugs and drug classes are not recommended for patients with any manifestation of Lyme disease. These treatments include (Lantos, et al., 2021):

- first generation cephalosporins, fluoroquinolones, aminoglycosides, pyrazinamide, vancomycin, tigecycline, metronidazole, tinidazole, rifampin, hydroxychloroquine, fluconazole
- 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

Lantos et al. (2015) highlighted additional unconventional treatments for Lyme disease that are not supported by scientific evidence which could cause harm:

- chelation
- electromagnetic therapy

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 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. (2001a). 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 ten 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 ten 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 ten days of oral placebo capsules; a placebo injection followed by ten days of oral doxycycline and then followed by ten 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 ten-day doxycycline group, and 86.5% in the doxycycline-ceftriaxone group. The authors concluded that "extending treatment with doxycycline from ten to 20 days or adding one dose of ceftriaxone to the beginning of a ten-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."

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. (2001a) 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 two to four 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
Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): these organizations published updated clinical practice guidelines for the prevention, diagnosis, and treatment of Lyme disease (Lantos, et al., 2021). The clinical practice guideline was endorsed by American Academy of Family Physicians, Association of Medical Microbiology and Infectious Disease Canada, Child Neurology Society, Pediatric Infectious Diseases Society, Entomological Society of America, and European Society of Clinical Microbiology and Infectious Diseases. The guidelines addressed the following questions for treatment of Lyme disease with antibiotics:

- What are the preferred antibiotic regimens for the treatment of erythema migrans?
  - For patients with erythema migrans, recommend using oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil (Strong recommendation, moderate-quality of evidence).
    - Comment: For patients unable to take both doxycycline and beta-lactam antibiotics, the preferred second-line agent is azithromycin.

- How long should a patient with erythema migrans be treated?
  - Recommend that patients with erythema migrans be treated with either a 10-day course of doxycycline or a 14-day course of amoxicillin or cefuroxime axetil rather than longer treatment courses (Strong recommendation, moderate-quality evidence).
    - Comment: If azithromycin is used, the indicated duration is five to ten days, with a seven day course preferred in the US, as this duration of therapy was used in the largest clinical trial performed in the US.

- Should patients with Lyme disease-related parenchymal involvement of the brain or spinal cord be treated with oral or IV antibiotics?
  - In patients with Lyme disease-associated parenchymal involvement of the brain or spinal cord, recommend using IV over oral antibiotics (Strong recommendation, moderate-quality evidence).

- What are the preferred antibiotic regimens for the treatment of acute neurologic manifestations of Lyme disease without parenchymal involvement of the brain or spinal cord?
  - In patients with Lyme disease-associated meningitis, cranial neuropathy, radiculoneuropathy, or with other PNS manifestations, recommend using intravenous (IV) ceftriaxone, cefotaxime, penicillin G, or oral doxycycline over other antimicrobials (Strong recommendation, moderate-quality evidence).
    - Comment: Decisions about the choice of antibiotic among these, including the route of administration, should primarily be made based on individual factors such as side effect profile, ease of administration, ability to tolerate oral medication, concerns about compliance unrelated to effectiveness. Treatment route may be changed from IV to oral during treatment. The preferred antibiotic duration is 14 to 21 days.

- What are the preferred antibiotic regimens for the initial treatment of Lyme arthritis?
  - For patients with Lyme arthritis, recommend using oral antibiotic therapy for 28 days (Strong recommendation, moderate-quality evidence).

- What are the preferred antibiotic regimens for the treatment of Lyme carditis?
  - In outpatients with Lyme carditis, suggest oral antibiotics over IV antibiotics (Weak recommendation, very low-quality evidence).
  - In the hospitalized patient with Lyme carditis, suggest initially using IV ceftriaxone over oral antibiotics until there is evidence of clinical improvement, then switching to oral antibiotics to complete treatment (Weak recommendation, very low-quality evidence).
  - For the treatment of Lyme carditis, suggest 14 to 21 days of total antibiotic therapy over longer durations of treatment (Weak recommendation, very low-quality evidence).
    - Comment: Oral antibiotic choices for Lyme carditis are doxycycline, amoxicillin, cefuroxime axetil, and azithromycin.

- What are the approaches to patients in whom Lyme arthritis has not completely resolved?
  - In patients with Lyme arthritis with partial response (mild residual joint swelling) after a first course of oral antibiotic, no recommendation for a second course of antibiotic is made versus observation (no recommendation, knowledge gap).
    - Comment: Consideration should be given to exclusion of other causes of joint swelling than Lyme arthritis, medication adherence, duration of arthritis prior to initial treatment, degree of synovial proliferation versus joint swelling, patient preferences, and cost. A second course of oral antibiotics for up to one month may be a reasonable alternative for patients in whom synovial proliferation is modest

compared to joint swelling and for those who prefer repeating a course of oral antibiotics before considering IV therapy.
  - In patients with Lyme arthritis with no or minimal response (moderate to severe joint swelling with minimal reduction of the joint effusion) to an initial course of oral antibiotic, we suggest a two to four week course of IV ceftriaxone over a second course of oral antibiotics (weak recommendation, low-quality evidence).

- How should post-antibiotic (previously termed antibiotic-refractory) Lyme arthritis be treated?
  - In patients who have failed one course of oral antibiotics and one course of IV antibiotics, suggest a referral to a rheumatologist or other trained specialist for consideration of the use of disease modifying antirheumatic drugs, biologic agents, intraarticular steroids, or arthroscopic synovectomy (Weak recommendation, very low-quality evidence).
    - Comment: Antibiotic therapy for longer than 8 weeks is not expected to provide additional benefit to patients with persistent arthritis if that treatment has included one course of IV therapy.

- Should patients with persistent symptoms following standard treatment of Lyme disease receive additional antibiotics?
  - For patients who have persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for Lyme disease, but who lack objective evidence of reinfection or treatment failure, recommend against additional antibiotic therapy (Strong recommendation, moderate-quality evidence).
    - Comment: Evidence of persistent infection or treatment failure would include objective signs of disease activity, such as arthritis, meningitis, or neuropathy.

- What is the preferred antibiotic regimen for the treatment of borrelial lymphocytoma?
  - In patients with borrelial lymphocytoma, suggest oral antibiotic therapy for 14 days (Weak recommendation, low-quality evidence).

- What is the preferred antibiotic regimen for the treatment of acrodermatitis chronica atrophicans?
  - In patients with acrodermatitis chronica atrophicans, suggest oral antibiotic therapy for 21 to 28 days over shorter durations (Weak recommendation, low-quality evidence).

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.

The American Academy of Pediatrics (Meissner, et al., 2020) published guidelines for the management of pediatric Lyme disease. Current guidelines for postexposure prophylaxis (or treatment) of Lyme borreliosis include the use of doxycycline regardless of age. Doxycycline traditionally has not been used in children <8 years of age because of concern about staining of permanent teeth. However, available data indicated this complication has not been associated with doxycycline, in contrast to older tetracyclines. Prophylactic antibiotic therapy is not recommended for a tick bite that is equivocal or considered low risk, but the person should be followed for development of erythema migrans or other manifestations of infection. A person with a potential tick exposure in an endemic area who develops erythema migrans should be treated on the basis of the clinical findings. Laboratory testing is not recommended because most people will be seronegative during the early stage of Lyme borreliosis.

Selection of an antimicrobial agent for the treatment of erythema migrans in pediatric patients (amoxicillin, doxycycline, cefuroxime axetil, or azithromycin) should consider the following:

- the presence of extracutaneous manifestations of infection, particularly neurologic involvement (for which doxycycline is the drug of choice)
- the ability to minimize sun exposure (photosensitivity)
- the frequency of administration (twice versus three times daily depending on the drug selected)
- and the likelihood of coinfection with Anaplasma phagocytophilum or an Ehrlichia muris–like agent (which are sensitive to doxycycline but not to β-lactam antibiotics)

In most circumstances, a child <8 years of age is treated with oral amoxicillin, and a patient >8 years of age is treated with oral doxycycline.

Pediatric patients with possible Lyme arthritis should undergo serum antibody testing rather than polymerase chain reaction or culture of blood or synovial tissue. For patients with Lyme arthritis, oral antibiotic therapy for 28 days is recommended. For patients with Lyme arthritis who have minimal or no response to the initial course of oral antibiotic therapy, a 2- to 4- week course of intravenous (IV) ceftriaxone is recommended over a second course of oral antibiotic.

An electrocardiogram is recommended for patients with signs or symptoms consistent with Lyme carditis, including dyspnea, edema, palpitations, lightheadedness, chest pain, or syncope. Hospitalized patients with Lyme carditis should be treated with IV ceftriaxone, followed by an oral antibiotic once evidence of clinical improvement is present. An outpatient with Lyme carditis may receive an oral antibiotic instead of an IV antibiotic.

For patients with Lyme borreliosis–associated meningitis or cranial neuropathy, oral antibiotic therapy with doxycycline is recommended over IV treatment due to ease of administration and a lower likelihood of adverse effects. For rare cases of Lyme encephalomyelitis (parenchymal involvement of the brain or spinal cord), IV ceftriaxone is recommended over oral antibiotic therapy. Routine use of corticosteroid therapy for children <16 years of age with cranial neuropathy is not recommended due to lack of evidence.

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 (Lantos, et al., 2021; National Institute of Allergy and Infectious Diseases [NIAID], 2018; 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 > 24 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).

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 (CDC, 2024; Wormser, et al., 2006).

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).

The IDSA guidelines include the following recommendations for the diagnosis, management, and treatment of babesiosis (Krause, et al., 2021).

- 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.
- 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 more than one month.
- All patients with active babesiosis should be treated with antimicrobial therapy because of the risk of complications.
- Recommended treatment:
  - The treatment combination of atovaquone plus azithromycin or the combination of clindamycin plus quinine is recommended for a duration of 7-10 days.

- 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 orally. 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, 600 mg every six hours intravenously or 600 mg every eight hours orally, and quinine, 650 mg every 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.
- 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.
- Exchange transfusion may be considered for patients with high-grade parasitemia (≥10%), or one or more of the following: 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.
  - In immunocompetent patients, monitoring Babesia parasitemia during treatment of acute illness using peripheral blood smears is recommended, but not for parasitemia once symptoms have resolved
  - In immunocompromised patients, monitoring Babesia parasitemia using peripheral blood smears even after they become asymptomatic and until blood smears are negative is recommended. PCR testing should be considered if blood smears have become negative, but symptoms persist.

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.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	No determination found.	
LCD		No determination found.	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
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

HCPCS Codes	Description
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-10-CM Diagnosis Codes	Description
A69.20-A69.29	Lyme disease
A77.40-A77.49	Ehrlichiosis
B60.00	Babesiosis, unspecified
B60.01	Babesiosis due to Babesia microti
B60.02	Babesiosis due to Babesia duncani
B60.03	Babesiosis due to Babesia divergens
B60.09	Other babesiosis
B60.8	Other specified protozoal diseases
B64	Unspecified protozoal disease

Considered Not Medically Necessary 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)

CPT®* Codes	Description
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

HCPCS Codes	Description
	all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10-CM Diagnosis Codes	Description
A69.20-A69.29	Lyme disease
A77.40-A77.49	Ehrlichiosis
B60.00	Babesiosis, unspecified
B60.01	Babesiosis due to Babesia microti
B60.02	Babesiosis due to Babesia duncani
B60.03	Babesiosis due to Babesia divergens
B60.09	Other 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 not medically necessary:

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, without imaging guidance; younger than 5 years of age
36569	Insertion of peripherally inserted central venous catheter (PICC), without subcutaneous port or pump, without imaging guidance; 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
36572	Insertion of peripherally inserted central venous catheter (PICC), without subcutaneous port or pump, including all imaging guidance, image documentation, and all associated radiological supervision and interpretation required to perform the insertion; younger than 5 years of age
36573	Insertion of peripherally inserted central venous catheter (PICC), without subcutaneous port or pump, including all imaging guidance, image documentation, and all associated radiological supervision and interpretation required to perform the insertion; age 5 years or older

CPT®* Codes	Description
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-10-CM Diagnosis Codes	Description
A69.20-A69.29	Lyme disease
A77.40-A77.49	Ehrlichiosis
B60.00	Babesiosis, unspecified
B60.01	Babesiosis due to Babesia microti
B60.02	Babesiosis due to Babesia duncani
B60.03	Babesiosis due to Babesia divergens
B60.09	Other babesiosis
B60.8	Other specified protozoal diseases
B64	Unspecified protozoal disease

ICD-10-CM Diagnosis Codes	Description
A69.20-A69.29	Lyme disease

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Revision Details

Type of Revision	Summary of Changes	Date
Annual review	• No clinical policy statement changes.	7/15/2024