Lyme Disease

Policy Number: INFECTIOUS 001.25
Effective Date: December 1, 2023

Instructions for Use

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Related Policies
None

Coverage Rationale

Note: This policy does not address the use of oral antibiotics which is the preferred regimen for initial treatment of confirmed Lyme Disease Associated Arthritis.

The use of parenteral antibiotics (in this case intravenous [IV] antibiotics), such as ceftriaxone, cefotaxime, penicillin G, or azithromycin (for individuals intolerant to betalactam antibiotics) for a period of up to 28 days is proven and may be medically necessary for treating:

- Individuals with acute neurologic manifestations or parenchymal involvement of the brain or spinal cord
- Individuals with Lyme carditis
- Individuals who have failed to respond to an initial course of oral antibiotics over a 2–4-week period with a persistent active infection demonstrated by serum antibody testing, culture or other bacteriologic techniques
- Individuals with Early Disseminated Lyme Disease (EDLD)
- Individuals with Late Neurologic Lyme Disease (LD)

A repeat course of parenteral antibiotics in individuals who have failed one course of oral antibiotics and one course of IV antibiotics is unproven and not medically necessary for treating Lyme Arthritis.

Due to insufficient evidence of efficacy and safety, other indications for parenteral antibiotic therapy for Lyme disease (LD) are considered unproven and not medically necessary including, but not limited to any of the following:

- Prophylactic treatment of individuals who have reported a tick bite but have no clinical findings suggestive of LD, or
- Treatment of individuals with systemic symptoms without serologic or cerebrospinal fluid (CSF) studies confirming LD
- Treatment of individuals with Post-Treatment Lyme Disease Syndrome (PTLDS) or Post-Lyme Disease Syndrome (PLDS)

Exception: Connecticut law requires coverage for confirmed Lyme Disease as treatment including not less than thirty days of intravenous antibiotic therapy, sixty days of oral antibiotic therapy, or both, and provides for further treatment if recommended by a licensed board-certified rheumatologist, infectious disease specialist, or neurologist.

Definitions

Early Disseminated Lyme Disease: Considered the second stage of Lyme disease (LD), it occurs a few weeks after the initial tick bite after the initial infection goes untreated. Individuals present with one or more of the following conditions: multiple erythema migrans lesions, Lyme carditis (LC), Lyme acute aseptic meningitis or Lyme-associated seventh paralysis. (Kowalski, et al. 2010)

Late Lyme Disease Associated Arthritis: Late LD arthritis will often develop in untreated patients at a mean time of 6 months after disease onset (range, 4 days to as long as 2 years). In untreated patients, Lyme arthritis is characterized by intermittent attacks of synovitis that last for a few weeks to several months. One or two joints are involved at a time. Primarily large joints are affected, but there may be involvement of the temporomandibular joint, small joints, and periarticular sites. The most commonly involved joint is the knee. Baker cysts may form and rupture. Joint swelling is often pronounced, but pain is usually relatively modest. (Wormser, 2020)

Late Neurologic Lyme Disease: Late neurologic LD may present as encephalomyelitis (characterized primarily by memory deficit, irritability and somnolence), peripheral neuropathy (presenting as intermittent limb paresthesia or radicular pain) or encephalopathy (manifested primarily by distal paresthesia or radicular pain).

Post-Treatment Lyme Disease Syndrome (PTLDS) or Post-Lyme Disease Syndrome (PLDS): Post-treatment Lyme Disease Syndrome (PTLDS) and Post-Lyme Disease Syndrome (PLDS) have been used to describe patients who remain ill following antibiotic treatment for Lyme disease. These two terms are frequently used interchangeably. PTLDS or PLDS occurs with onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6-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. (Lantos, 2015)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

HCPCS Code	Description
J0456	Injection, azithromycin, 500 mg
J0558	Injection, penicillin G benzathine and penicillin G procaine, 100,000 units
J0561	Injection, penicillin G benzathine, 100,000 units
J0696	Injection, ceftriaxone sodium, per 250 mg
J0698	Injection, cefotaxime sodium, per g
J2510	Injection, penicillin G procaine, aqueous, up to 600,000 units
J2540	Injection, penicillin G potassium, up to 600,000 units

Description of Services

Lyme disease (LD) is caused by the bacteria (spirochete), *Borrelia burgdorferi (Bb)*, which lives in the gut of *Ixodes* ticks. Ticks become infected with Bb while feeding on an infected host, typically rodents. The bacteria are transmitted to humans via the

saliva of a feeding tick. According to the 2020 Clinical Practice Guidelines on Lyme Disease published by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR), a tick bite is considered to be high risk only if it meets the following 3 criteria: the tick bite was from (a) an identified Ixodes spp. vector species, (b) it occurred in a highly endemic area, and (c) the tick was attached for ≥ 36 hours.

LD is a progressive disease that can occur in three stages: early localized, early disseminated and late. Early localized LD, or stage I, occurs in the weeks following the bite of an infected tick. The first sign of LD is a characteristic bull's eye rash, called erythema migrans, which forms at the site of the tick bite in the majority of cases. The second stage of LD, called early disseminated LD (EDLD), is characterized by multiple erythema migrans lesions (that typically occur days to weeks after infection) and/or neurologic and/or cardiac findings (that typically occur weeks to months after infection). The bacteria spread from the primary site via cutaneous, lymphatic and hematogenous routes, causing general signs and symptoms of infection and organ involvement. Late LD (third stage) is usually associated with intermittent or persistent arthritis and/or neurologic problems. Late LD may develop months to a few years after the initial infection. Individuals with late LD may not have noticed or recall early localized or EDLD. Late LD can have a variety of manifestations including encephalitis, encephalomyelitis, cerebral arteritis, polyneuropathy and arthritis. For the majority of individuals these symptoms improve gradually over six months to a year with antibiotic treatment.

A small number of individuals report a variety of non-specific symptoms such as generalized pain, joint pain or fatigue following an episode of LD that has been appropriately treated with antibiotics. These patients often show no evidence of an active infection. If symptoms persist for more than 6 months after standard treatment the condition is often termed Post-Lyme Disease Syndrome (PLDS), or chronic LD where symptomatic treatment is recommended rather than ongoing or repeat antibiotic therapy. (IDSA; Wormser, et al., 2006/2010; Wormser, 2020)

Clinical Evidence

Available evidence supports that early LD with no indication of neurologic or cardiac involvement is best treated with oral antibiotics. Evidence supports the clinical consensus that the indications for parenteral antibiotics are generally limited to Lyme arthritis that failed to respond to oral therapy, late neurologic Lyme disease, Lyme carditis requiring hospitalization, and Lyme meningitis or radiculopathy requiring hospitalization. [American Academy of Neurology (AAN) / America College of Rheumatology (ACR) / Infectious Diseases Society of America (IDSA), 2020]

Evidence does not support the use of any antibiotic (oral or parenteral) for PTLDS, PLDS, or prophylactic treatment of individuals who have reported a tick bite with equivocal risk or low risk and has no clinical findings suggestive of LD.

Arnason and Skogman (2022) completed a retrospective observational study to evaluate clinical outcomes in children who had received intravenous ceftriaxone as compared to children who had received oral doxycycline as antibiotic treatment for Lyme neuroborreliosis (LNB). Clinical and laboratory data from three previously conducted prospective studies on children with LNB (1998–2014) was used. A total of 321 children (1–19 years of age), who received antibiotic treatment for definite LNB or possible LNB, were included. Clinical outcome at the 2-month follow-up (recovery/nonrecovery) was evaluated using Chi2 test and logistic multivariate regression analysis. Out of 321 LNB patients, 194 children (60%) had received ceftriaxone and 127 children (40%) had received doxycycline. When comparing clinical outcomes between the treatment groups, no difference was found (p = 0, 217). Results did not change when incorporating relevant clinical and laboratory data into the logistic multivariate regression analysis. The authors concluded that in this large retrospective study, no difference in clinical outcome was found, independent of age, when comparing children who received ceftriaxone with those who received doxycycline, supporting an equal effectiveness for treatment of pediatric patients with LNB. However, future randomized comparative treatment studies are warranted for evaluation of efficacy of antibiotic treatment in pediatric patients with LNB.

Kortela et al. (2021) completed a multicenter, equivalence RCT aimed at assessing whether oral doxycycline is equally effective as intravenous ceftriaxone in the treatment of LNB. Between 14 September 2012 and 28 December 2017, 210 adults with suspected LNB were assigned to receive doxycycline (n = 104) or ceftriaxone (n = 106). The per-protocol analysis comprised 82 patients with doxycycline and 84 patients with ceftriaxone. In the per-protocol analysis, the mean change in the VAS score was −3.9 in the doxycycline group and −3.8 in the ceftriaxone group (mean difference, 0.17 [95% confidence interval, −.59 to .92], which was within the prespecified equivalence margins of −1 to 1 units). Findings of the intention-to-treat analyses were similar. Participants in both groups improved equally. The authors concluded oral doxycycline is equally effective as intravenous ceftriaxone in the treatment of LNB.

To investigate whether longer-term antibiotic treatment improves cognitive performance in patients with persistent symptoms attributed to Lyme borreliosis, Berende, et al. (2019) collected data during the Persistent Lyme Empiric Antibiotic Study Europe (PLEASE) trial, a randomized, placebo-controlled study. Study participants passed performance-validity testing (measure for detecting suboptimal effort) if they had persistent symptoms attributed to Lyme borreliosis. All patients received a 2-week open-label regimen of intravenous ceftriaxone before the 12-week blinded oral regimen (doxycycline, clarithromycin/hydroxychloroquine, or placebo). Cognitive performance was assessed at baseline and after 14, 26, and 40 weeks with neuropsychological tests covering the cognitive domains of episodic memory, attention/working memory, verbal fluency, speed of information processing, and executive function. The authors concluded that a 2-week treatment with ceftriaxone followed by a 12-week regimen of doxycycline or clarithromycin/hydroxychloroquine did not lead to better cognitive performance compared to a 2-week regimen of ceftriaxone in patients with Lyme disease-attributed persistent symptoms. The study provided Class II evidence that longer-term antibiotics in patients with borreliosis-attributed persistent symptoms does not increase cognitive performance compared to shorter-term antibiotics.

In earlier findings of the same randomized, double-blind, placebo-controlled trial, Berende et al. (2016) assessed whether long-term antibiotic treatment of persistent symptoms attributed to LD led to better outcomes than short-term treatment. Patients were randomly assigned to receive a 12-week oral course of doxycycline (n = 86), clarithromycin plus hydroxychloroquine (n = 96) or placebo (n = 98). All patients received intravenous (IV) ceftriaxone daily for 2 weeks before initiating the randomized regimen. The primary outcome measure was health-related quality of life (QOL) at the end of the treatment period at week 14, after the 2-week course of ceftriaxone and the 12-week course of the randomized study drug or placebo had been completed. Of the 281 patients who underwent randomization, 280 were included in the modified intention-to-treat analysis. The authors reported that long-term antibiotic treatment did not have additional beneficial effects on health related QOL beyond those seen with short-term treatment. The rates of adverse events (AEs) were similar among the study groups.

Cadavid et al. (2016) reviewed seven randomized studies involving 450 European participants with LNB in adults and children that compared any antibiotic treatment, including combinations of treatments, versus any other treatment, placebo, or not treatment. The trials investigated four antibiotics: penicillin G and ceftriaxone in four studies, doxycycline in three studies, and cefotaxime in two studies. The authors concluded that none of the studies provided clear evidence that one antibiotic was better than another and treatment with any of the four antibiotics produced similarly good outcomes for treatment of neurological LD in Europe. Two comparisons reported in this review are particular interest to this policy: Comparison 2. Oral doxycycline versus intravenous ceftriaxone for LNB (acute and chronic) and Comparison 3. Intravenous penicillin G versus oral doxycycline for LNB (acute and chronic). Neither of these comparisons showed superiority of one approach compared to the other. The authors concluded that these randomized studies provided some evidence that doxycycline, penicillin G, ceftriaxone, and cefotaxime are efficacious in the treatment of European LNB. In addition, no evidence of additional efficacy was observed when, in one study, an initial antibiotic treatment with intravenous ceftriaxone was followed by additional longer treatment with oral amoxicillin. The authors concluded there was a lack of evidence identified through this research on the efficacy of antibiotics for treatment of LNB in the United States.

Fallon et al. (2008) studied patients with mild to moderate cognitive impairment and marked levels of fatigue, pain, and impaired physical functioning. Patients had well-documented LD, with at least 3 weeks of prior IV antibiotics, current positive IgG Western blot, and objective memory impairment. Healthy individuals served as controls for practice effects. 37 patients were randomly assigned to 10 weeks of double-masked treatment with IV ceftriaxone or IV placebo and then no antibiotic therapy. Across six cognitive domains, a significant treatment-by-time interaction favored the antibiotic-treated group at week 12. The improvement was generalized (not specific to domain) and moderate in magnitude, but it was not sustained to week 24. On secondary outcome, patients with more severe fatigue, pain, and impaired physical functioning who received antibiotics were improved at week 12, and this was sustained to week 24 for pain and physical functioning. IV ceftriaxone therapy resulted in short-term cognitive improvement for patients with posttreatment Lyme encephalopathy, but relapse in cognition occurred after the antibiotic was discontinued.

Klempner et al. (2001) reported two RCTs, which appear to overlap with the RCTs reported by Kaplan et al. (2003), of extended antibiotic treatment for the patients in whom symptoms persisted after the recommended treatment (n = 129) and evaluated QOL outcomes. Seventy-eight patients who were seropositive for IgG antibodies and 51 patients who were seronegative were randomized to receive either IV ceftriaxone daily for 30 days, followed by oral doxycycline daily for 60 days or matching IV and oral placebos. After completion of treatment with antibiotics, 37 percent of the seropositive group showed improvement in the physical- and mental- component summary scales of the Short-Form General Health Survey, 29 percent had no change, and 34 percent had a worsening of symptoms. In the seropositive patients who received placebo, 40 percent improved, 26 percent had

no change, and 34 percent worsened. The results were similar for the seronegative patients in both treatment groups. The authors concluded that for the entire population in these two trials, treatment with intravenous and oral antibiotics for 90 days dd not improve symptoms more than placebo.

Safety

Available evidence suggests that prolonged use of parenteral antibiotics for treating LD does not improve treatment outcomes and is associated with an increased incidence of adverse events. In June 2017, the Centers for Disease Control and Prevention (CDC) released a warning about potential severe and life-threatening bacterial infections associated with various treatments for chronic LD. The warning notes that several RCTs have shown that prolonged courses of IV antibiotics, in particular, do not substantially improve long-term outcome for patients with a diagnosis of chronic LD and can result in serious harm, including death. (Marzec et al., 2017)

Results of available RCTs not only failed to demonstrate a prolonged therapeutic effect of long-term antibiotic therapy for chronic LD; they also demonstrated a serious risk of harm. High rates of AEs following long-term antibiotic therapy were observed. One study reported that diarrhea occurred more often following antibiotic therapy than placebo treatment (43% versus 25%), and another study reported that rash, diarrhea, and vaginal pruritus occurred more frequently after antibiotic treatment than placebo (14% versus 3%). More serious, life-threatening complications were also reported in some individuals, including anaphylaxis in one patient (Krupp et al., 2003), life-threatening pulmonary embolism in one patient, and anemia accompanied by fever and gastrointestinal bleeding in one patient. (Klempner et al., 2001)

Clinical Practice Guidelines

American Academy of Neurology (AAN)/American College of Rheumatology (ACR)/Infectious Diseases Society of America (IDSA)

In late 2020, an evidence-based clinical practice guideline for the prevention, diagnosis, and treatment of Lyme disease was developed by a multidisciplinary panel representing the Infectious Diseases Society of America (IDSA), the American Academy of Neurology (AAN), and the American College of Rheumatology (ACR). The scope of the guideline includes prevention of Lyme disease, and the diagnosis and treatment of Lyme disease presenting as erythema migrans, Lyme disease complicated by neurologic, cardiac, and rheumatologic manifestations, Eurasian manifestations of Lyme disease, and Lyme disease complicated by coinfection with other tickborne pathogens. The guidelines state that under most circumstances, oral therapy is effective and preferred over intravenous therapy due to equivalent efficacies, tolerability, and cost. However, indications for intravenous therapy, such as treatment in the hospitalized patient, are discussed. The guidelines make the following recommendations: (Lantos et al., November 2020)

- Prophylactic antibiotic therapy may be given only to adults and children within 72 hours of removal of an identified high-risk tick bite, but not for bites that are equivocal risk or low risk (strong recommendation, high-quality evidence). If a tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended. A tick bite is considered to be high risk only if it meets the following 3 criteria: the tick bite was from (a) an identified Ixodes spp. vector species, (b) it occurred in a highly endemic area, and (c) the tick was attached for ≥ 36 hours.
- For high-risk tick bites in all age groups, the administration of a single dose of oral doxycycline within 72 hours of tick removal is recommended over observation (strong recommendation, moderate-quality evidence). Doxycycline is advised as a single oral dose, 200 mg for adults and 4.4 mg/kg (up to a maximum dose of 200 mg) for children.
- For patients with erythema migrans, use of oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil is recommended (strong recommendation; moderate quality of evidence). Additionally, it was noted that for patients unable to take both doxycycline and beta-lactam antibiotics, the preferred second line agent is azithromycin. It is recommended that patients with erythema migran 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. If azithromycin is used, the indicated duration is 5-10 days, with a 7-day course preferred in the United States.
- In patients with Lyme disease–associated meningitis, cranial neuropathy, radiculoneuropathy, or with other peripheral nervous system (PNS) manifestations, IV antibiotics are recommended using ceftriaxone, cefotaxime, penicillin G, or oral doxycycline over other antimicrobials. (strong recommendation, moderate-quality evidence). However, it was noted that 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, and 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, the guidelines support using IV over oral antibiotics (strong recommendation, moderate-quality evidence).
- The preferred antibiotic regimens for the treatment of Lyme carditis include the following recommendations:
  - Oral antibiotics over IV antibiotics in outpatients with Lyme carditis (weak recommendation, very-low-quality evidence).
  - In the hospitalized patient with Lyme carditis, we suggest initially using IV ceftriaxone over oral antibiotics until there is evidence of clinical improvement and then switching to oral antibiotics to complete treatment (weak recommendation, very-low-quality evidence).
  - For the treatment of Lyme carditis, we suggest 14–21 days of total antibiotic therapy over longer durations of treatment (weak recommendation, very-low-quality evidence).
- For patients with Lyme arthritis, using oral antibiotic therapy for 28 days is the preferred antibiotic regimen for the initial treatment.
- For patients in whom Lyme arthritis has not completely resolved, the following are guidelines are recommended related to antibiotic use:
  - In patients with Lyme arthritis with partial response (mild residual joint swelling) after a first course of oral antibiotic, the panel makes no recommendation for a second course of antibiotic vs observation (no recommendation, knowledge gap). Consideration should be given to exclusion of other causes of joint swelling than Lyme arthritis, medication adherence, duration of arthritis before initial treatment, degree of synovial proliferation vs joint swelling, patient preferences, and cost. A second course of oral antibiotics for up to 1 month may be a reasonable alternative for patients in whom synovial proliferation is modest compared with 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, the panel suggests a 2- to 4-week course of IV ceftriaxone over a second course of oral antibiotics (weak recommendation, low-quality evidence).
- In patients who have failed 1 course of oral antibiotics and 1 course of IV antibiotics, a referral is recommended to a rheumatologist or other trained specialist for consideration of the use of disease modifying antirheumatic drugs (DMARDs), biologic agents, intra-articular steroids, or arthroscopic synovectomy (weak recommendation, very-low-quality evidence). Antibiotic therapy for longer than 8 weeks is not expected to provide additional benefit to patients with persistent arthritis if that treatment has included 1 course of IV therapy.
- 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, the guidelines advise against additional antibiotic therapy (strong recommendation, moderate-quality evidence). Evidence of persistent infection or treatment failure would include objective signs of disease activity, such as arthritis, meningitis, or neuropathy.
- Oral antibiotic therapy for 14 days is suggested for treating borrlial lymphocytoma (weak recommendation, low-quality evidence).
- In patients with acrodermatitis chronica atropicans, oral antibiotic therapy for 21-28 days over shorter durations is suggested (weak recommendation, low-quality evidence).

It should be noted that although several of the recommendations are supported by low to moderate quality evidence, in the informed opinion expressed by the AAN, ACR and IDSA in the 22020 guideline represent the prevailing consensus of the expert practicing community responsible for the treatment of individuals with LD.

Centers for Disease Control and Prevention (CDC)

In 2021, the CDC posted guidance on antibiotic treatment of Neurologic Lyme Disease indicating facial palsy is treated with oral antibiotics and Lyme meningitis/radiculoneuritis can either be treated with oral doxycycline or IV ceftriaxone, depending on severity. Oral therapy can be substituted when the patient is stabilized or discharged to complete the course. Most people with Lyme disease respond well to antibiotics and fully recover. Varying degrees of permanent nervous system damage may develop in people who do not receive treatment in the early stages of illness and who develop late-stage Lyme disease.

In November 2019, the CDC posted guidance on the treatment of Post-Treatment Lyme Disease Syndrome (PTLDS) indicating that patients with PTLDS usually get better over time, but it can take many months to feel completely well. The CDC indicates there is no proven treatment for PTLDS. Although short-term antibiotic treatment is a proven treatment for early Lyme disease, studies funded by the National Institutes of Health (NIH) have found that long-term outcomes are no better for patients who received additional prolonged antibiotic treatment than for patients who received placebo. Long-term antibiotic treatment for

Lyme disease has been associated with serious, sometimes deadly complications, as described in studies conducted by Goodlet and Fairman (2018); Marzec et al. (2017); De Wilde et al. (2017); Holzbauer et al. (2010), and Patel et al. (2000).

National Institute of Allergy and Infectious Diseases (NIAID)

In November 2018, the NIAID published their findings from three placebo-controlled clinical trials to learn more about the efficacy of prolonged antibiotic therapy for treating post-treatment Lyme disease syndrome (PTLDS). These trials were designed to ensure that several key parameters were addressed:

- The susceptibility of B. burgdorferi, the bacterium that causes Lyme disease, to specific antibiotics.
- The ability of antibiotics to cross the blood-brain barrier, access the central nervous system, and persist at effective levels throughout the course of therapy.
- The ability of antibiotics to kill bacteria living both outside and inside mammalian cells.
- The safety and welfare of patients enrolled in the trials, including improvements in self-reported fatigue and cognitive function.

In all three studies, people receiving prolonged antibiotic therapy reported a greater improvement in fatigue than those in placebo; however, no benefit to cognitive function was observed. In one of the studies, 26% of the individuals experienced AEs attributed to intravenous antibiotic use; whereas in another study, 11% experienced AEs. The NIAID findings reported that carefully designed, placebo-controlled studies have failed to demonstrate that prolonged antibiotic therapy is beneficial.

A reappraisal of several of these studies concluded that IV antibiotics may provide benefit to PTLDS fatigue, but in light of significant adverse events they were not recommended, and improved methods of treatment were needed. Another study challenged the interpretation of the results on statistical grounds, a position not accepted by the study authors. Individuals therefore continue to debate whether additional antibiotic treatment trials are needed, or if the lack of benefit from such an approach is settled science.

National Institute for Health and Care Excellence (NICE)

In April 2018, NICE published a guideline that covered diagnosing and managing Lyme disease (LD) with the aim of raising awareness of when Lyme disease should be suspected and ensure that individuals have prompt and consistent diagnosis and treatment. The guideline includes specific antibiotic treatment based on symptoms with oral doxycycline, amoxicillin or azithromycin or intravenous ceftriaxone for LD in adults and young people (aged 12 and over) versus LD in children (under 12). Intravenous antibiotics for 21 days are recommended as a first line of treatment for patients 9 and older with LD affecting the central nervous system and individuals if all ages with Lyme carditis and hemodynamically unstable. Otherwise, oral antibiotics are recommended as a first line of treatment. When an oral switch is being considered, use of doxycyline is recommended. The standard duration of treatment ranged from 21 to 28 days, depending on symptoms, age and whether intravenous antibiotics was administered as an alternate treatment. The committee also made recommendations that individuals who present with ongoing for LD symptoms should not be routinely offered more than 2 courses of antibiotics because of lack of evidence of benefit. The committee noted the importance of considering alternative diagnoses to prevent inappropriate antibiotic treatment and misdiagnosis. Discussion with a specialist or referral should be considered if a different tick-borne disease is possible.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Several parenteral antibiotics used in the treatment of Lyme disease are approved by the FDA. Although these antibiotics have broad-spectrum activity, they are not specifically approved for use in *B. burgdorferi* infections. Search the following website for additional information. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. (Accessed August 2, 2023)

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Policy History/Revision Information

Date	Summary of Changes
12/01/2023	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version INFECTIOUS 001.24

Instructions for Use

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.