

LYME DISEASE

Policy Number: INFECTIOUS 001.18 T2

Effective Date: December 1, 2018

[Instructions for Use](#) ⓘ

Table of Contents	Page
CONDITIONS OF COVERAGE	1
COVERAGE RATIONALE	1
APPLICABLE CODES	2
DESCRIPTION OF SERVICES	2
DEFINITIONS	2
CLINICAL EVIDENCE	2
U.S. FOOD AND DRUG ADMINISTRATION	6
REFERENCES	6
POLICY HISTORY/REVISION INFORMATION	7
INSTRUCTIONS FOR USE	8

Related Policies
None

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes ²
Precertification with Medical Director Review Required	No ^{1,2}
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Home, Outpatient, Office
Special Considerations	<p>¹Medical Director review is required only for treatment lasting beyond a period of 28 days. Exceptions may apply (see Coverage Rationale).</p> <p>²Participating Providers in the Office Setting: Precertification is required for services performed in the office of a participating provider. Non-Participating/Out-of-Network Providers in the Office Setting: Precertification is not required, but is encouraged for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.</p>

COVERAGE RATIONALE

The use of parenteral antibiotics, such as ceftriaxone, cefotaxime or penicillin G, for a period of up to 28 days is proven and medically necessary for treating early disseminated Lyme disease (LD).

Available evidence supports that early LD with no indication of neurologic or cardiac involvement is treated with oral antibiotics.

Continuous treatment lasting longer than 28 days or a repeat course of parenteral antibiotics beyond 28 days is unproven and not medically necessary for treating LD except in individuals with [Late Neurologic Lyme Disease](#) and late LD associated arthritis. Beyond this, no clinical evidence supports ongoing or repeat antibiotic treatment for these late LD manifestations.

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.

Exception for Connecticut Commercial Members

Precertification is **not** required for the use of parenteral antibiotics, regardless of treatment length/timeframe, when referred or recommended by a board certified rheumatologist, infectious disease specialist and/or neurologist. (CT Ins. Code 38A-518H and 38A-492H)

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
J0558	Injection, penicillin G benzathie and penicillin G procaine, 100,000 units
J0561	Injection, penicillin G benzathine, 100,000 units
J0696	Injection, ceftriaxone sodium, per 250 mg
J0698	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.

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, 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). Some individuals have no antecedent early localized LD. 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. Late LD may not be preceded by a history of early localized or early disseminated LD. 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.

A small number of individuals report a variety of non-specific symptoms such as generalized pain, joint pain or fatigue following an episode of Lyme disease that has been appropriately treated with antibiotics. If symptoms persist for more than 6 months after standard treatment, the condition is often termed post-Lyme disease syndrome (PLDS), or Chronic Lyme Disease where symptomatic treatment is recommended rather than ongoing or repeat antibiotic therapy. (IDSA; Wormser, et al., 2006/2010)

DEFINITIONS

Late Neurologic Lyme Disease: Late Neurologic Lyme disease 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).

CLINICAL EVIDENCE

Short Term Antibiotic Treatment

Several clinical practice guidelines recommend the use of short term parenteral antibiotic treatment (≤ 4 weeks) in patients with specific Lyme disease manifestations (see [Professional Societies](#) information below). These

recommendations are based on a high quality body of evidence, derived from a number of randomized controlled trials (RCTs), which demonstrate the safety and efficacy for this indication.

Long Term Antibiotic Treatment

In a randomized, double-blind, placebo-controlled trial, Berende et al. (2016) assessed whether long-term antibiotic treatment of persistent symptoms attributed to Lyme disease 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 were similar among the study groups. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01207739) number NCT01207739.

Four additional randomized, placebo-controlled, double-blinded clinical trials, published as three studies, evaluated antibiotic therapy in patients with chronic Lyme disease. All RCTs were sponsored by the National Institutes of Health (NIH). Patients were either untreated or had failed primary antibiotic treatment. Study size was generally small, and ranged from 37 to 78 patients. Patients were administered IV ceftriaxone for a treatment duration that ranged from 28 days to 3 months. One study also administered oral doxycycline for 60 days following 30 days of IV ceftriaxone. Outcome measures were varied, and included biological markers of infection, functional status and/or Health-Related Quality of Life (HR-QOL) measures, cognitive function, mood and psychological measures, fatigue, and pain. These studies, including outcomes measures and treatment results are described in detail below.

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 Lyme disease, 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.

Krupp et al. (2003) conducted a single-center randomized double-masked placebo-controlled trial on 55 patients with Lyme disease with persistent severe fatigue at least 6 or more months after antibiotic therapy. Patients were randomly assigned to receive 28 days of IV ceftriaxone or placebo. The primary clinical outcomes were improvement in fatigue and cognitive function. The primary laboratory outcome was measure of infection. Outcome data were collected at the 6-month visit. Ceftriaxone therapy in patients with post-Lyme syndrome (PLS) with severe fatigue was associated with an improvement in fatigue but not with cognitive function or laboratory measure of infection. 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) studied 129 patients in two randomized double-blind placebo-controlled studies of patients with a history of post-treatment chronic LD to determine whether antibiotic therapy improved cognitive function. Patients received IV ceftriaxone 2 g daily for 30 days followed by oral doxycycline 200 mg daily for 60 days or matching IV and oral placebos. Assessments were made at 90 and 180 days after treatment. The authors concluded that patients with post-treatment chronic Lyme disease who have symptoms (e.g., fatigue, depression) but show no evidence of persisting *Borrelia* infection do not show objective evidence of cognitive impairment. Additional antibiotic therapy was not more beneficial than administering placebos. Added expense and toxicity are the only proven results of such practice. Iatrogenic problems, such as gallbladder disease, fungal infections, and other superinfections, and gastrointestinal problems, certainly increase with prolonged use of broad-spectrum antibiotics. This highlights the need for an appropriate diagnosis before subjecting the patient to antibiotic regimens.

Klempner et al. (2001) conducted two RCTs of extended antibiotic treatment for the same set 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.

Klempner et al. (2013) stated that the authors of 4 National Institutes of Health-sponsored antibiotic treatment trials of patients with persistent unexplained symptoms despite previous antibiotic treatment of Lyme disease determined that re-treatment provided little if any benefit and carries significant risk. Two groups recently provided an independent re-assessment of these trials and concluded that prolonged courses of antibiotics are likely to be helpful. These investigators have carefully considered the points raised by these groups, along with their own critical review of the treatment trials. On the basis of this analysis, the authors concluded that there is a meaningful clinical benefit to be gained from re-treatment of such patients with parenteral antibiotic therapy cannot be justified.

Cadavid et al. (2016) reviewed seven randomized studies involving 450 European participants with Lyme neuroborreliosis (LNB) in adults and children that compared antibiotic treatment, including combinations of treatments, versus any other treatment, placebo, or no 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 Lyme disease in Europe. A second treatment with amoxicillin did not appear to provide added benefit to ceftriaxone.

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 with oral doxycycline, amoxicillin or azithromycin or intravenous ceftriaxone for LD in adults and young people (aged 12 and over) according to symptoms versus antibiotic treatment and doses for LD in children (under 12). The standard duration of treatment ranged from 21 to 28 days, depending on symptoms and age. The committee determined that longer courses of 21 days of treatment should be offered as a standard because of their concern at low cure rates at less than 21 days in some studies and the lack of clear evidence for shorter courses. 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.

Safety

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 Lyme disease. 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 Lyme disease 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 Lyme disease, they also demonstrated a serious risk of harm. High rates of adverse events 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)

Professional Societies

American Academy of Neurology (AAN)

In 2007, the Quality Standards Subcommittee (QSS) of the AAN published evidenced-based practice parameters for the treatment of nervous system Lyme disease. (Halperin et al., 2007) Recommendations in the QSS/AAN practice parameters include:

- 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.
- Recommended duration of both oral and parenteral regimens is 14 days, although the duration of antibiotic therapy in published studies ranged from 10 to 28 days without significantly different outcomes.
- Prolonged courses of antibiotics do not provide beneficial effects in post-Lyme syndrome (PLDS), and antibiotics are potentially associated with adverse events.

European Federation of Neurological Societies (EFNS)

An EFNS guideline on the diagnosis and management of Lyme disease makes the following recommendations (Mygland et al., 2010):

- Adult patients with definite or possible acute Lyme disease (symptom duration <6 months) should be offered a single 14-day course of antibiotic treatment. Oral doxycycline (200 mg daily) and IV ceftriaxone (2 g daily) are equally effective in patients with symptoms confined to the peripheral nervous system, including meningitis (level A).
- Patients with central nervous system manifestations should be treated with IV ceftriaxone (2 g daily) for 14 days and late Lyme disease (symptom duration >6 months) for 3 weeks.
- Children should be treated as adults, except that doxycycline is contraindicated under 8 years of age (nine in some countries).
- If symptoms persist for more than 6 months after standard treatment, the condition is often termed post-Lyme disease syndrome (PLDS). Antibiotic therapy has no impact on PLDS.

Infectious Diseases Society of America (IDSA)

IDSA guidelines for the treatment of Lyme disease make the following recommendations (Wormser et al., 2006; deemed current 2018):

- In the absence of neurologic or cardiac manifestations, oral antibiotics (e.g., doxycycline, amoxicillin or cefuroxime axetil) are recommended for 14 to 21 days. Doxycycline is recommended for 10-21 days of treatment. Amoxicillin and cefuroxime axetil are recommended for 14-21 days of treatment. IV antibiotics, while effective, are not superior to oral agents and are more likely than the recommended orally administered antimicrobials to cause serious adverse effects. Therefore, IV antibiotics are not recommended for treatment of patients with early Lyme disease and no indication of neurologic or cardiac involvement.
- For patients with early Lyme disease and acute neurologic manifestations of meningitis or radiculopathy, the use of IV ceftriaxone for 14 days, with a range of 10 to 28 days is recommended. Parenteral therapy with cefotaxime or penicillin G may be a satisfactory alternative.
- Patients with atrioventricular heart block and/or myopericarditis associated with early Lyme disease may be treated with either oral or parenteral antibiotic therapy for 14 to 21 days.
- Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally. Doxycycline, amoxicillin or cefuroxime axetil for 28 days is recommended. However, it is important to recognize that a small number of patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require IV therapy with a beta-lactam antibiotic for successful resolution.
- Patients with arthritis plus objective evidence of neurologic disease should receive parenteral therapy with ceftriaxone for 14 to 28 days. Cefotaxime or penicillin G administered parenterally is an acceptable alternative.
- Patients who have persistent or recurrent joint swelling after a recommended course of oral antibiotic therapy should be retreated with another 4-week course of oral antibiotics OR with a 2 to 4 week course of IV ceftriaxone. A second 4-week course of oral antibiotic therapy is favored by panel members for the patient whose arthritis has substantively improved but has not yet completely resolved, reserving IV antibiotic therapy for those patients whose arthritis failed to improve at all or worsened. Clinicians should consider waiting several months before initiating retreatment with antimicrobial agents because of the anticipated slow resolution of inflammation after treatment.
- Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone for 14 to 28 days. Cefotaxime or penicillin G administered intravenously is an alternative. Response to treatment is usually slow and may be incomplete. Retreatment is not recommended unless relapse is shown by reliable objective measures.
- Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (≥ 6 months) subjective symptoms after administration of recommended treatment regimens for Lyme disease.
- Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data or the potential for harm to the patient, long-term (> 28 days) antibiotic therapy is not recommended for treatment of patients with any manifestation of Lyme disease.
- Multiple, repeated courses of antimicrobials for the same episode of Lyme disease is not recommended.

In 2008, a review panel was convened to determine whether the IDSA's guidelines were based on sound scientific evidence and whether revisions were needed. Based on its review of all the evidence, the review panel determined that no changes or revisions to the 2006 IDSA guidelines were necessary. The panel's conclusions, which are consistent with those reached by the IDSA as well as other societies, represent the state of medical science at the time of writing. Only high-quality, prospective, controlled clinical trial data demonstrating both benefit and safety will be sufficient to change the current recommendations. (Lantos et al., 2010)

After reviewing the evidence, the panel presented the following conclusions regarding antibiotic therapy for patients with chronic symptoms after recommended treatment regimens for Lyme disease. (Lantos et al., 2010)

- The prospective, controlled clinical trials for extended antibiotic treatment of Lyme disease have demonstrated considerable risk of harm, including potentially life-threatening adverse events.

- Prospective, controlled clinical trials have demonstrated little benefit from prolonged antibiotic therapy.
- The risk/benefit ratio from prolonged antibiotic therapy strongly discourages prolonged antibiotic courses for Lyme disease.

International Lyme and Associated Diseases Society (ILADS)

ILADS published updated evidence-based guidelines for the management of Lyme disease. The recommendations regarding antibiotic retreatment are based on very low quality evidence. Clinicians should discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease. These discussions should provide patient-specific risk–benefit assessments for each treatment option. While continued observation alone is an option for patients with few manifestations, minimal QOL impairments and no evidence of disease progression, in the panel’s judgment, antibiotic retreatment will prove to be appropriate for the majority of patients who remain ill. Prior to instituting antibiotic retreatment, the original Lyme disease diagnosis should be reassessed and clinicians should evaluate the patient for other potential causes of persistent disease manifestations. The presence of other tick-borne illnesses should be investigated if that had not already been done. When antibiotic retreatment is undertaken, clinicians should initiate treatment with 4–6 weeks of the selected antibiotic. Clinicians should re-assess patients immediately following the completion of the initial course of retreatment to evaluate the effectiveness of retreatment and the need for therapeutic adjustments. In cases where the patient does not improve after 4–6 weeks of antibiotic retreatment, clinicians should reassess the clinical diagnosis as well as the anticipated benefit. They should also confirm that other potential causes of persistent manifestations have been adequately investigated prior to continuing antibiotic retreatment. (Cameron et al., 2014)

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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 3, 2018)

REFERENCES

- Berende A, ter Hofstede HJ, Vos FJ, et al. Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. *N Engl J Med*. 2016 Mar 31;374(13):1209-20.
- Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. *Expert Rev Anti Infect Ther*. 2014 Sep;12(9):1103-35.
- Centers for Disease Control and Prevention (CDC). Lyme disease diagnosis. Health Topics A-Z. Atlanta, GA: CDC; October 7, 2005. Available at: http://www.cdc.gov/ncidod/dvbid/lyme/ld_human_disease_diagnosis.htm. Last updated December 1, 2017. Accessed July 30, 2018.
- Cadavid D, Awaerter PG, Rumaugh J, Gelderblom H. Antibiotics for the neurological complications of Lyme Disease. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No.: CD006978. DOI: 10.1002/141858.CD006978.pub2.
- Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology*. 2008 Mar 25; 70(13):992-1003.
- Halperin JJ, Shapiro ED, Logigian E, et al. Practice parameter: Treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2007 Jul 3; 69(1):91-102.
- Hayes, Inc. Medical Technology Directory. Intravenous antibiotic treatment for late-stage Lyme disease. August 2010a. Updated July 2014. Archived September, 2015.
- Hayes, Inc. Medical Technology Directory. Long-term antibiotic therapy for chronic Lyme disease. December 2010b. Updated January 2014. Archived January, 2016.
- Hayes, Inc. News-Clinical Study. Treatment of Persistent Lyme Disease Revisited. September 5, 2012.
- Infectious Disease Society of America (ISDA). Updated Guidelines on Diagnosis, Treatment of Lyme Disease. October 2, 2006. Available at: <https://academic.oup.com/cid/article/43/9/1089/422463>. Accessed August 1, 2018.
- Institute of Medicine (IOM). Committee on Lyme Disease and Other Tick-Borne Diseases: The State of the Science. Critical needs and gaps in understanding prevention, amelioration, and resolution of Lyme and other tick-borne diseases: the short-term and long-term outcomes. Workshop Report. Washington (DC): National Academies Press; 2011. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK57020/>. Accessed July 30, 2018.

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

Klempner MS, Baker PJ, Shapiro ED, et al. Treatment trials for post-Lyme disease symptoms revisited. *Am J Med*. 2013;126(8):665-669.

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

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

Lantos PM, Charini WA, Medoff G, et al. Final report of the Lyme disease review panel of the Infectious Diseases Society of America. *Clin Infect Dis*. 2010 Jul 1; 51(1):1-5.

Marzec NS, Nelson C, Waldron PR, et al. Serious bacterial infections acquired during treatment of patients given a diagnosis of chronic Lyme disease - United States. *MMWR Morb Mortal Wkly Rep*. 2017 Jun 16;66(23):607-609.

Mygland A, Ljøstad U, Fingerle V, et al.; European Federation of Neurological Societies. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neurol*. 2010 Jan; 17(1):8-16, e1-4.

National Institute for Health and Care Excellence (NICE). NICE guideline: Lyme disease. 11 April 2018; updated July 2018. ISBN: 978-1-4731-2919-1. Available at: <https://www.nice.org.uk/guidance/ng95>. Accessed July 31, 2018.

Wormser G, Dattwyler R, Shapiro E, et al. The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2006; 43:1089-1134. Errata October 2007; 45: 941. Available at: <https://academic.oup.com/cid/article/43/9/1089/422463>. Reaffirmed 2010.

Wormser GP, Ramanathan R, Nowakowski J, et al. Duration of antibiotic therapy for early Lyme disease. *Ann Intern Med*. 2003; 138:697-704.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
12/01/2018	<ul style="list-style-type: none"> • Reorganized policy template: <ul style="list-style-type: none"> ○ Simplified and relocated <i>Instructions for Use</i> ○ Removed <i>Benefit Considerations</i> section • Updated conditions of coverage/special considerations; modified notation to clarify: <ul style="list-style-type: none"> ○ For participating providers in the office setting: Precertification is required for services performed in the office of a participating provider ○ For non-participating/out-of-network providers in the office setting: Precertification is not required, but is encouraged for out-of-network services performed in the office; if precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered • Revised coverage rationale: <ul style="list-style-type: none"> ○ Replaced language indicating: <ul style="list-style-type: none"> ▪ “The use of parenteral antibiotics, such as ceftriaxone, cefotaxime or penicillin G, for a period of up to 28 days is proven and medically necessary for treating Lyme disease” with “the use of parenteral antibiotics, such as ceftriaxone, cefotaxime or penicillin G, for a period of up to 28 days is proven and medically necessary for treating <i>early disseminated</i> Lyme disease (<i>LD</i>); <i>available evidence supports that early LD with no indication of neurologic or cardiac involvement is treated with oral antibiotics</i>” ▪ “The use of parenteral antibiotics beyond 28 days is unproven and not medically necessary treating LD” with “<i>continuous treatment lasting longer than 28 days or a repeat course of parenteral antibiotics beyond 28 days is unproven and not medically necessary for treating LD except in individuals with Late Neurologic Lyme Disease and late LD associated arthritis; beyond this, no clinical evidence supports ongoing or repeat antibiotic treatment for these late LD manifestations</i>” ○ Added language to clarify available evidence suggests that prolonged use of parenteral antibiotics <i>for treating LD</i> does not improve treatment outcomes and is associated with an increased incidence of adverse events ○ Removed additional information indicating:

Date	Action/Description
	<ul style="list-style-type: none"> ▪ Patients with objective signs of relapse, after receiving recommended antibiotic therapy, may need a second course of treatment <ul style="list-style-type: none"> - Experts recommend waiting several months before initiating retreatment because of the anticipated slow resolution of inflammation after treatment - Retreatment with parenteral antibiotics is not recommended except in patients with late neurologic Lyme disease - Multiple, repeated courses of antimicrobials for the same episode of Lyme disease are not recommended ▪ If patients have no resolution of arthritis after completion of a course of antibiotics, and if polymerase chain reaction (PCR) results for a sample of synovial fluid or tissue are negative for <i>B. burgdorferi</i> nucleic acids, symptomatic treatment is recommended <ul style="list-style-type: none"> - Symptomatic therapy might consist of nonsteroidal anti-inflammatory agents (NSAIDs), intra-articular injections of corticosteroids or disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine <ul style="list-style-type: none"> • Updated list of applicable HCPCS codes; added J0558 and J0561 • Added definition of "Late Neurologic Lyme Disease" • Updated supporting information to reflect the most current description of services, clinical evidence, and references • Archived previous policy version INFECTIOUS 001.17 T2

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 MCG™ Care Guidelines, 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.