

# LYME DISEASE

Policy Number: 2016T0351N

Effective Date: October 1, 2016

Table of Contents	Page
<a href="#">INSTRUCTIONS FOR USE</a> .....	1
<a href="#">BENEFIT CONSIDERATIONS</a> .....	1
<a href="#">COVERAGE RATIONALE</a> .....	1
<a href="#">APPLICABLE CODES</a> .....	2
<a href="#">DESCRIPTION OF SERVICES</a> .....	2
<a href="#">CLINICAL EVIDENCE</a> .....	2
<a href="#">U.S. FOOD AND DRUG ADMINISTRATION (FDA)</a> .....	5
<a href="#">CENTERS FOR MEDICARE AND MEDICAID SERVICES</a> .....	5
<a href="#">REFERENCES</a> .....	5
<a href="#">POLICY HISTORY/REVISION INFORMATION</a> .....	6

<b>Community Plan Policy</b>
• <a href="#">Lyme Disease</a>
<b>Medicare Advantage Coverage Summary</b>
• <a href="#">Medications/Drugs (Outpatient/Part B)</a>

## INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines 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.

## BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

### **Essential Health Benefits for Individual and Small Group**

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

## 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 Lyme disease.**

**The use of parenteral antibiotics beyond 28 days is unproven and not medically necessary for treating Lyme disease.**

Available evidence suggests that prolonged use of parenteral antibiotics does not improve treatment outcomes and is associated with an increased incidence of adverse events.

## **Additional Information**

Patients with objective signs of relapse, after receiving recommended antibiotic therapy, may need a second course of treatment. 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 disease. Multiple, repeated courses of antimicrobials for the same episode of Lyme disease are not recommended (Wormser et al., 2006; deemed current 2011).

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 *B. burgdorferi* nucleic acids, symptomatic treatment is recommended. Symptomatic therapy might consist of nonsteroidal anti-inflammatory agents (NSAIDs), intra-articular injections of corticosteroids or disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine (Wormser et al., 2006; deemed current 2011).

## **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 and Coverage Determination Guidelines may apply.

HCPCS Code	Description
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

*CPT® is a registered trademark of the American Medical Association*

## **DESCRIPTION OF SERVICES**

Lyme disease (LD) is caused by the bacterial 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, 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 disseminated LD or stage II LD, occurs in the weeks to 6 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. Untreated LD that has progressed for more than 6 months is called late LD, late disseminated LD or stage III LD. Late LD can have a variety of manifestations including encephalitis, encephalomyelitis, cerebral arteritis, polyneuropathy and arthritis. All stages of LD are treated with antibiotics.

## **CLINICAL EVIDENCE**

### **Short Term Antibiotic Treatment**

Several clinical practice guidelines recommend the use of short term parental antibiotic treatment ( $\leq 4$  weeks) in patients with Lyme disease (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 ceftriaxone daily for 2 weeks before initiating the randomized regimen. The primary outcome measure was health-related quality of life 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 quality of life beyond those seen with short-term treatment. The rates of adverse events were similar among the study groups. ClinicalTrials.gov 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 intravenous (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 intravenous (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 outcomes, 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.

Klempner et al. (2001) conducted two RCTs of extended antibiotic treatment for the same set of patients in whom symptoms persisted after the recommended treatment (n=129) and evaluated quality of life (QOL) outcomes. Seventy-eight patients who were seropositive for IgG antibodies and 51 patients who were seronegative were randomized to receive either intravenous ceftriaxone daily for 30 days, followed by oral doxycycline daily for 60 days or matching intravenous 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.

Subsequently, Kaplan et al. (2003) evaluated the same 129 patients enrolled in the Klempner et al. (2001) study, and reported neurocognitive outcomes following additional antibiotic therapy. Symptom severity was measured using the cognitive functioning, pain and role functioning scales of the Medical Outcomes Study (MOS). Memory, attention and executive functioning were assessed using objective tests. Mood was assessed using the Beck Depression Inventory (BDI) and Minnesota Multiphasic Personality Inventory (MMPI). There were no significant baseline differences between seropositive and seronegative groups. Both groups reported a high frequency of MOS symptoms, depression and somatic complaints but had normal baseline neuropsychological test scores. The combined groups showed significant decreases in MOS symptoms, higher objective test scores and improved mood between baseline and 90 days. However, there were no significant differences between those receiving antibiotics and placebo. Patients with PTCLD who had symptoms but showed no evidence of persisting *Borrelia* infection, did not show objective evidence of cognitive impairment. Additional antibiotic therapy was not more beneficial than administering placebo.

## **Safety**

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 (reaffirmed 2014), 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 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 intravenous (IV) ceftriaxone (2 g daily) are equally effective in patients with symptoms confined to the peripheral nervous system, including meningitis.
- 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.
- 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 2011):

- In the absence of neurologic or cardiac manifestations, oral antibiotics (e.g. doxycycline, amoxicillin or cefuroxime axetil) are recommended for 14 to 21 days. Intravenous (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 ceftriaxone for 14 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. However, it is important to recognize that a small number of patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require intravenous 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 intravenous 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 intravenous 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. Retreatments 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 ( $\geq 6$  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 quality of life 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 5, 2016.

### **CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not have a National Coverage Determination (NCD) for the treatment of Lyme disease. Local Coverage Determinations (LCDs) do not exist at this time.

Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at <http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf>.

(Accessed August 5, 2016)

### **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. Available at: <http://www.ilads.org/lyme/treatment-guideline.php>. Accessed August 5, 2016.
- ECRI Institute. Hotline Response. Antibiotic therapy for treating Lyme disease. November 2014. Report archived.

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. Reaffirmed April 2014.

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.

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: <http://www.ncbi.nlm.nih.gov/books/NBK57020/>. Accessed August 5, 2016.

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, 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.

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.

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

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. Deemed current as of October 2011. Available at: <http://cid.oxfordjournals.org/content/43/9/1089.full.pdf>. Accessed August 5, 2016.

#### POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
10/01/2016	<ul style="list-style-type: none"><li>• Reformatted and reorganized policy; transferred content to new template</li><li>• Updated coverage rationale:<ul style="list-style-type: none"><li>○ Modified references to applicable timeframes for use of parenteral antibiotics; replaced "4 weeks" with "28 days"</li></ul></li><li>• Updated supporting information to reflect the most current description of services, clinical evidence, CMS information, and references</li><li>• Archived previous policy version 2015T0351M</li></ul>