LYME DISEASE

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COVERAGE RATIONALE

The use of parenteral antibiotics, such as ceftriaxone, cefotaxime or penicillin G, for a period up to 4 weeks is proven for treating Lyme disease.

The use of parenteral antibiotics beyond 4 weeks is unproven 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).

Lyme Disease: Medical Policy (Effective 10/01/2013)

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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).

**BENEFIT CONSIDERATIONS**

State mandates should be reviewed when determining coverage for the treatment of Lyme disease.

**BACKGROUND**

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.

Some studies consider an additional stage of LD called chronic LD, post-LD syndrome or posttreatment LD syndrome (PTLDs). This stage refers to those few patients who either relapse after primary treatment, experience fatigue, cognitive dysfunction and musculoskeletal pain despite adequate antibiotic treatment of the initial disease, or who appear not to respond to treatment (Hayes, 2010a; updated 2011).

**CLINICAL EVIDENCE**

**Short Term Antibiotic Treatment**

Several clinical practice guidelines recommend the use of short term parental antibiotic treatment (≤ 4 weeks) in patients with Lyme disease (Please see Professional Societies). 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**

Four 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.

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Safety

High rates of adverse events following long-term antibiotic therapy have been observed in the available studies. 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; Hayes, 2010b; updated 2012).

Summary

Results of the available RCTs not only failed to demonstrate a prolonged therapeutic effect of long term antibiotic therapy for chronic Lyme disease, and but they also demonstrated a serious risk of harm. The overall body of evidence was of moderate quality, with individual study quality varying from fair to good. However, the evidence is hampered by the small number of available studies, variation in outcome measures across studies, and high dropout rates in some studies. There was some evidence that long-term antibiotic therapy might improve fatigue and conflicting evidence that the treatment might improve neurocognitive measures. However, there was no evidence of the efficacy of antibiotic treatment to improve patient-relevant outcomes, such as functional status and/or quality of life, pain, mood, and psychological measures. Furthermore, there was a high rate of treatment-related adverse events associated with long-term antibiotic therapy, some of which were considered serious and life-threatening. Definitive patient selection criteria for long-term antibiotic therapy for chronic LD have not been established (Hayes, 2010b; updated 2012).

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. Recommendations include (Halperin et al., 2007):

- Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for CNS Lyme disease with or without parenchymal involvement.
- 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):

• 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. 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):

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

2. Prospective, controlled clinical trials have demonstrated little benefit from prolonged antibiotic therapy.

3. The risk/benefit ratio from prolonged antibiotic therapy strongly discourages prolonged antibiotic courses for Lyme disease.

International Lyme and Associated Diseases Society (ILADS)
In 2004, ILADS published evidence-based guidelines for the management of Lyme disease. Review of the duration of treatment found that due to disappointing long-term outcomes with shorter courses of antibiotics, the practice of stopping antibiotics to allow for a delayed recovery is no longer recommended for patients with persistent, recurrent and refractory Lyme disease. Reports show failure rates of 30-62% within 3 years of short course treatment using antibiotics thought to be effective for Lyme disease. Conversely for neurologic complications of Lyme disease, doubling the length of intravenous ceftriaxone treatment from 2 to 4 weeks improved the success rate from 66 to 80%. The management of chronic Lyme disease must be individualized, since patients will vary according to severity of presentation and response to previous treatment. Concurrent risk factors (i.e., co-infections, previous treatment failures, frequent relapses, neurologic involvement, or previous use of corticosteroids) or evidence of unusually severe Lyme disease should lead to the initiation of prolonged and/or intravenous antibiotic treatment. Physicians should always assess the patient's response to treatment before deciding on appropriate duration of therapy (i.e., weeks versus months) (Cameron et al., 2004).

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. See the following website for additional information. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed July 23, 2013.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for the pharmacological treatment of Lyme disease. Local Coverage Determinations (LCDs) do not exist at this time. Lyme Disease: Medical Policy (Effective 10/01/2013)
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 July 25, 2013)

APPLICABLE CODES

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

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REFERENCES


**POLICY HISTORY/REVISION INFORMATION**

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