Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

Policy # 00173
Original Effective Date: 07/15/2005
Current Effective Date: 09/21/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider a 2 to 4 week course of intravenous (IV) antibiotic therapy for the treatment of Lyme disease (LD) to be eligible for coverage for the following conditions:

(Note: Treatment for Lyme disease (LD) consists of oral antibiotics unless the following diagnoses are confirmed)

- Neuroborreliosis with objective neurologic complications of documented Lyme disease (LD); or
- Lyme carditis; or
- Well-documented Lyme arthritis.

Patient Selection Criteria
Coverage eligibility will be considered for the following diagnoses when confirmed as outlined below:

Neuroborreliosis
Neuroborreliosis requires documentation of the following:

- Documentation of all of the following objective neurologic complications:
  - Lymphocytic meningitis with documented cerebrospinal fluid (CSF) abnormalities; and
  - Cranial neuropathy, other than uncomplicated cranial nerve palsy, with documented cerebrospinal fluid (CSF) abnormalities; and
  - Encephalitis or encephalomyelitis with documented cerebrospinal fluid (CSF) abnormalities; and
  - Radiculopathy; and
  - Polyneuropathy.

Lyme disease may be documented either on the basis of serologic testing or by clinical findings of erythema migrans in early infection. Documentation of cerebrospinal fluid (CSF) abnormalities is required for suspected central nervous system (CNS) infection, as indicated above.

Serologic documentation of infection requires:

- Positive or indeterminate enzyme-linked immunosorbent assay (ELISA) test; and
- Positive immunoblot by Centers for Disease Control and Prevention (CDC) criteria.
Documented cerebrospinal fluid (CSF) abnormalities include all of the following:

- Pleocytosis;
- Evidence of intrathecal production of *Borrelia burgdorferi* (B. burgdorferi) antibodies in cerebrospinal fluid (CSF); and
- Increased protein levels

**Lyme Carditis**

A 2 to 4 week course of intravenous (IV) antibiotic therapy may be eligible for coverage in patients with Lyme carditis. Documentation of the following is required:

- Positive serologic findings (defined above)
- A high degree of atrioventricular block or a PR interval of >0.3 sec

Documentation of Lyme carditis may include PCR-based direct detection of *B. burgdorferi* in the blood when results of serologic studies are equivocal.

**Lyme Arthritis**

A single 2 to 4 week course of intravenous (IV) antibiotic therapy may be eligible for coverage in the small subset of patients with well-documented Lyme arthritis who have the following:

- Severe arthritis requiring the rapid response associated with intravenous (IV) antibiotics; and
- Documentation of Lyme arthritis may include polymerase chain reaction (PCR)-based direct detection of *B. burgdorferi* in the synovial tissue or fluid when results of serologic studies are equivocal

Based on review of available data, the Company may consider polymerase chain reaction (PCR)-based direct detection of *B. burgdorferi* in cerebrospinal fluid (CSF) samples to be eligible for coverage and may replace serologic documentation of infection in patients with a short duration of neurologic symptoms (<14 days) during the window between exposure and production of detectable antibodies.

**When Services Are Considered Investigational**

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers repeat polymerase chain reaction (PCR)-based direct detection of *B. burgdorferi* in cerebrospinal fluid (CSF) samples to be investigational:

- As a justification for continuation of intravenous (IV) antibiotics beyond one month in patients with persistent symptoms
- As a technique to follow therapeutic response

Based on review of available data, the Company considers polymerase chain reaction (PCR)-based direct detection of *B. burgdorferi* in urine samples in all clinical situations to be investigational.

Based on review of available data, the Company considers genotyping or phenotyping of *B. burgdorferi* to be investigational.
Based on review of available data, the Company considers other diagnostic testing including but not limited to C6 peptide ELISA or determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment to be investigational.*

Based on review of available data, the Company considers intravenous (IV) antibiotic therapy in the following situations to be investigational*:

- Patients with symptoms consistent with chronic fatigue syndrome or fibromyalgia;
- Patients with seronegative Lyme disease (LD) in the absence of cerebrospinal fluid (CSF) antibodies;
- Initial therapy in patients with Lyme arthritis without coexisting neurologic symptoms;
- Cranial nerve palsy (e.g. Bell’s palsy) without clinical evidence of meningitis;
- Antibiotic-refractory Lyme arthritis (unresponsive to 2 courses of oral antibiotics or to 1 course of oral and 1 course of intravenous (IV) antibiotic therapy);
- Patients with vague systemic symptoms without supporting serologic or (CSF) studies;
- Patients with a positive enzyme-linked immunosorbent assay (ELISA) test, unconfirmed by an immunoblot or Western blot test;
- Patients with an isolated positive serologic test in the setting of multiple negative serologic studies;
- Patients with chronic (less than six months) subjective symptoms (“post-Lyme syndrome”) after receiving recommended treatment regimens for documented Lyme disease (LD);
- Repeat or prolonged courses (greater than four weeks) of antibiotic therapy;
- When patient selection criteria are not met.

Background/Overview

Lyme disease is a multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi* and transmitted by the bite of an infected ixodid tick endemic to Northeastern, North Central, and Pacific coastal regions of the U.S. The disease is characterized by stages, beginning with localized infection of the skin (erythema migrans), followed by dissemination to many sites. Manifestations of early disseminated disease may include lymphocytic meningitis, facial palsy, painful radiculoneuritis, atrioventricular nodal block, or migratory musculoskeletal pain. Months to years later, the disease may be manifested by intermittent oligoarthritis; particularly involving the knee joint, chronic encephalopathy, spinal pain, or distal paresthesias. While most manifestations of LD can be adequately treated with oral antibiotics, IV antibiotics are indicated in some patients with neurologic involvement or atrioventricular heart block. However, overdiagnosis and overtreatment of LD are common due to its nonspecific symptoms, a lack of standardization of serologic tests, and difficulties in interpreting serologic test results. In particular, patients with chronic fatigue syndrome or fibromyalgia are commonly misdiagnosed as possibly having LD and undergo inappropriate IV antibiotic therapy. The purpose of this policy is to provide diagnostic criteria for the appropriate use of IV antibiotic therapy. The following paragraphs describe the various manifestations of LD that may prompt therapy with IV antibiotics and the various laboratory tests that are used to support the diagnosis of LD.

Neurologic Manifestations of Lyme Disease (Neuroborreliosis)

Lymphocytic meningitis, characterized by head and neck pain, may occur during the acute disseminated stage of the disease. Analysis of the CSF is indispensable for the diagnosis of Lyme meningitis. If the
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In a patient with LD, the CSF will show a lymphocytic pleocytosis (lymphocyte count greater than normal) with increased levels of protein. Intrathecal production of antibodies directed at spirochetal antigens is typically present. A normal CSF analysis is strong evidence against Lyme meningitis. Treatment with a 2 to 4 week course of IV antibiotics, typically ceftriaxone or cefotaxime, is recommended.

Cranial neuritis, most frequently Bell’s palsy, may present early in the course of disseminated LD, occasionally prior to the development of antibodies, such that an LD etiology may be difficult to confirm. While Bell’s palsy typically resolves spontaneously with or without treatment with oral antibiotics, some physicians have recommended a lumbar puncture and a course of IV antibiotics if pleocytosis in the CSF is identified, primarily as a prophylactic measure to prevent further neurologic symptoms.

A subacute encephalopathy may occur months to years after disease onset, characterized by subtle disturbances in memory, mood, sleep or cognition accompanied by fatigue. These symptoms may occur in the absence of abnormalities in the electroencephalogram (EEG), magnetic resonance imaging (MRI) or CSF. In addition, the symptoms are nonspecific and overlap with fibromyalgia and chronic fatigue syndrome. Thus diagnosis of Lyme encephalopathy may be difficult and may be best diagnosed with a mental status exam or neuropsychological testing. However, treatment with IV antibiotics is generally not indicated unless CSF abnormalities are identified.

Much rarer but of greater concern is the development of encephalomyelitis, characterized by spastic paraparesis, ataxias, cognitive impairment, bladder dysfunction and cranial neuropathy. Cerebrospinal fluid examination reveals a pleocytosis and an elevation in protein. Selective synthesis of anti-spirochetal antigens can also be identified. A course of IV antibiotics with 3 to 4 weeks of ceftriaxone is suggested when CSF abnormalities are identified.

Much rarer but of greater concern is the development of encephalomyelitis, characterized by spastic paraparesis, ataxias, cognitive impairment, bladder dysfunction and cranial neuropathy. Cerebrospinal fluid examination reveals a pleocytosis and an elevation in protein. Selective synthesis of anti-spirochetal antigens can also be identified. A course of IV antibiotics with 3 to 4 weeks of ceftriaxone is suggested when CSF abnormalities are identified.

A variety of peripheral nervous system manifestations of LD have also been identified. Symptoms of peripheral neuropathy include paresthesias or radicular pain with only minimal sensory signs. Patients typically exhibit electromyographic (EMG) or nerve-conduction velocity abnormalities. Cerebrospinal fluid abnormalities are usually seen only in those patients with a coexistent encephalopathy.

Cardiac Manifestations of Lyme Disease
Lyme carditis may appear during the early dissemination stage of the disease. Symptoms include atrioventricular heart block, tachyarrhythmias and myopericarditis. Antibiotics are typically given, although no evidence proves that this therapy hastens the resolution of symptoms. Both oral and IV regimens have been advocated. Intravenous regimens are typically used in patients with a high-degree atrioventricular block or a PR interval on the electrocardiogram (EKG) of greater than 0.3 second. Patients with milder forms of carditis may be treated with oral antibiotics.

Lyme Arthritis
Lyme arthritis is a late manifestation of infection and is characterized by an elevated IgG response to B. burgdorferi and intermittent attacks of oligoarticular arthritis, primarily in the large joints such as the knee. Patients with Lyme arthritis may be successfully treated with a 30-day course of oral doxycycline or amoxicillin, but care must be taken to exclude simultaneous CNS involvement requiring IV antibiotic
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treatment. In the small subset of patients that do not respond to oral antibiotics, an additional 30-day course of oral or IV antibiotics may be recommended.

Fibromyalgia and Chronic Fatigue Syndrome
Fibromyalgia and chronic fatigue syndrome are the diseases most commonly confused with LD. Fibromyalgia is characterized by musculoskeletal complaints, multiple trigger points, difficulty in sleeping, generalized fatigue, headache or neck pain. The joint pain associated with fibromyalgia is typically diffuse in contrast to Lyme arthritis, which is characterized by marked joint swelling in one or a few joints at a time with few systemic symptoms. Chronic fatigue syndrome is characterized by multiple subjective complaints, such as overwhelming fatigue, difficulty in concentration, and diffuse muscle and joint pain. In contrast to LD, both of the above conditions lack joint inflammation, have normal neurological test results or have test results suggesting anxiety or depression. Neither fibromyalgia nor chronic fatigue syndrome has been shown to respond to antibiotic therapy.

Serologic Tests
The antibody response to infection with B. burgdorferi follows a typical pattern. During the first few weeks after the initial onset of infection, there is no antibody production. The specific IgM response characteristic of acute infection peaks between the third and sixth week. The specific IgG response develops only after months and includes antibodies to a variety of spirochetal antigens. IgG antibodies produced in response to LD may persist for months or years, thus detection of IgG antibodies only indicates exposure, either past or present. In LD endemic areas, underlying asymptomatic seropositivity may range up to 5%–10%. Thus, as with any laboratory test, interpretation of serologic tests requires close correlation with the patients’ signs and symptoms. For example, patients with vague symptoms of LD, chronic fatigue syndrome or fibromyalgia may undergo multiple serologic tests over many weeks to months in an effort to establish the diagnosis of LD. Inevitably, in this setting of repeat testing, one ELISA or test, whether IgG or IgM, may be reported as weakly positive or indeterminate. These results most likely represent false-positive test results in the uninfected patient who has had long-standing symptoms from a different condition and previously negative test results.

Currently, the CDC recommends a two-step method for the serologic diagnosis of LD.

ELISA for Borrelia burgdorferi Antibodies
This test is a screening serologic test for LD. Enzyme-linked immunosorbent assay tests are available to detect IgM or IgG antibodies or to detect both antibody types together. More recently developed tests using recombinant or synthetic antigens have improved diagnostic sensitivity. For example, the U.S. Food and Drug Administration (FDA)-approved C6 ELISA is highly sensitive to infection and is under study as an indicator of antibiotic therapy efficacy. A positive or indeterminate ELISA test result alone is inadequate serologic evidence of LD. All of these tests must be confirmed with an immunoblot test. In addition, as with any laboratory test, results must be correlated with the clinical picture.

Western Immunoblot
This test is used to confirm the serologic diagnosis of LD in patients with positive or indeterminate ELISA tests. In contrast to the standard ELISA test, the immunoblot investigates the specific antibody response to
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the different antigens of \textit{B. burgdorferi}. Typically, several clinically significant antigens are tested. According to Centers CDC criteria, the test result is considered positive if 2 of the 3 most common IgM antibody bands to spirochetal antigens are present, or 5 of the 10 most frequent IgG antibody bands are present. Because the CDC criteria were developed for surveillance, they are conservative and may miss true LD cases. Some support the use of more liberal criteria for a positive result in clinical diagnosis; however, alternative criteria have not been well validated. Criteria for interpreting immunoblot results are different in Europe than in the United States due to differences in prevalent \textit{Borrelia} species causing disease.

Other tests include the following.

\textbf{Polymerase Chain Reaction}

In contrast to the above 2 serologic tests, which only indirectly assess prior or present exposure to \textit{B.
burgdorferi}, PCR directly tests for the presence of the spirochete. Because PCR technology involves amplification of deoxyribonucleic acid (DNA) from a portion of \textit{B. burgdorferi}, there is a high risk of exogenous contamination, resulting in false-positive results. Positive results in the absence of clear clinical indicators or positive serology are not definitive for diagnosis. In addition, the test cannot distinguish between live spirochetes or fragments of dead ones. The PCR technique has been studied using a variety of specimens. PCR has the best detection rates for skin biopsies from patients with erythema migrans (but may not be indicated with recent history of tick bite or exposure) and for synovial tissue (and synovial fluid, to a lesser extent) from patients with Lyme arthritis. Cerebrospinal fluid may be positive by PCR during the first 2 weeks of infection, but thereafter the detection rate is low. Polymerase chain reaction is not recommended for urine or blood specimens. However, PCR-based direct detection of \textit{B. burgdorferi} in the blood may be useful for documenting Lyme carditis when results of serologic studies are equivocal.

\textit{Borrelia} PCR also provides information on which of the three major species pathogenic for humans has been found in the specimen tested (genotyping).

\textbf{T-Cell Proliferative Assay}

T-lymphocyte proliferation assays are not recommended as diagnostic tests. They are difficult to perform and standardize and their sensitivity is not well characterized.

\textbf{Evaluation of the Cerebrospinal Fluid}

Aside from the standard evaluation of CSF for pleocytosis, protein levels and glucose levels, various tests are available to determine whether anti-\textit{B. burgdorferi} antibodies are being selectively produced within the CSF. Techniques include a variety of immunoassays. For example, intrathecal antibody production can be detected by the CSF/serum index of \textit{B. burgdorferi} antibodies, CSF and serum samples diluted to match the total IgG concentration in CSF are run in parallel in an IgG ELISA. Excess \textit{Borrelia}-specific antibody in CSF indicates a positive result. As noted, PCR can also be used to detect the spirochete in the CSF, most successfully within the first two weeks of infection.

\textbf{Evaluation of the Chemoattractant CXCL13}

CXCL13 is a B lymphocyte chemoattractant and has been reported to be elevated in acute neuroborreliosis and a potential marker for successful treatment.
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Treatment of Lyme Disease
As noted above, treatment with IV antibiotics is generally indicated only in patients with symptoms and laboratory findings consistent with CNS or peripheral neurologic involvement and in a small subset of patients with heart block or documented Lyme arthritis who have not responded to oral antibiotics. Typical IV therapy consists of a 2 to 4 week course of ceftriaxone or cefotaxime, both third-generation cephalosporins, or penicillin or chloramphenicol. No data suggest that prolonged or repeated courses of IV antibiotics are effective. Lack of effect should suggest an incorrect diagnosis or slow resolution of symptoms, which is commonly seen in LD. In addition, some symptoms may persist after treatment, such as Lyme arthritis; this phenomenon may be related to various self-sustaining inflammatory mechanisms rather than persistent infection.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratory testing for Lyme disease is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. As of 2014, there were at least 70 approved commercial laboratories that perform serologic testing for Lyme disease. To date, the FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
The most recent literature search for this policy was performed through September 21, 2015. The following is a summary of the key literature to date.

Direct Detection of Borrelia burgdorferi with PCR Technology
While diagnosis of LD is generally based on the clinical picture and demonstration of specific antibodies, PCR-based technology can detect the spirochete in the CSF in cases of neuroborreliosis, in the synovial fluid of cases of Lyme arthritis, and rarely in skin biopsy specimens of those with atypical dermatologic manifestations. However, a PCR-based test is generally considered a second tier test, performed only when the results of serologic tests and clinical evaluation are equivocal. For example, while PCR-based tests can identify organisms in skin biopsy specimens of patients with dermatologic manifestations (i.e., erythema migrans), this diagnosis is typically made clinically and antibiotic therapy is started empirically. A skin biopsy is rarely necessary. Similarly, diagnosis of Lyme arthritis is based on clinical and serologic studies without the need for synovial tissue or fluid. Finally, intrathecal antibody production is considered a more sensitive test than PCR-based CSF detection in patients with suspected neuroborreliosis, but a PCR-based technique may be useful in patients with a short duration of disease (i.e., less than 14 days) during the window between exposure and the emergence of detectable levels of antibodies in the CSF. However, it should be noted that that the test cannot distinguish between live and dead organisms. PCR-based
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detection is typically not performed in the urine due to the variable presence of endogenous polymerase inhibitors that have an impact on the test's sensitivity.

PCR-based technology has been used as one step in the genotypic analysis of Borrelia burgdorferi. B burgdorferi was originally characterized as a single species (B burgdorferi sensu lato), but genotypic analysis has revealed that this group represents 3 distinct species and genomic groups. Of these, the following have been isolated from patients with LD: B burgdorferi sensu stricto, B garinii, and B afzelii. The prevalence of these different genospecies may vary among populations and may be associated with different clinical manifestations. However, no data were found in the published literature regarding whether or how knowledge of the genotype or phenotype of B burgdorferi could be used to improve patient management and outcomes. In the U.S., B burgdorferi sensu stricto is the only human pathogenic species, but in Europe, all 3 species cause infection. Recently, a new human pathogenic species, B spielmanii, was found in a small number of European patients; therefore, criteria for interpreting immunoblot results are different in Europe than in the U.S.

Chemokine CXCL13 and Other Diagnostic Tests
CXCL13 is a B lymphocyte chemoattractant that has been reported to be elevated in acute neuroborreliosis; thus it is a potential marker for successful treatment. However, data are limited. Additional research is necessary to determine diagnostic and treatment utility.

Other diagnostic testing strategies, such as enzyme immunoassay (EIA) using the C6 peptide, have not demonstrated improvements in specificity over the 2-tiered testing approach of ELISA followed by the Western blot. Branda and colleagues reported on the use of whole-cell sonicate EIA (ELISA) followed by C6 EIA and found the specificity and positive predictive values were comparable to the 2-tiered ELISA-Western blot approach (99.5% vs. 98.4%, and 70% vs. 66%, both respectively). Additional research is necessary to determine the validity and interpretation of study results and the value of using the 2-tiered EIA approach over the current standard of EIA (ELISA) followed by Western blot.

Role of Intravenous Antibiotics
A diagnosis of LD requires appropriate epidemiologic data, supporting clinical observation (including exposure to ixodid ticks in an endemic area), and supporting laboratory findings. However, overdiagnosis and overtreatment of LD is common. Intravenous antibiotic therapy in patients with presumed LD would be inappropriate in the following situations: an incorrect diagnosis; a history of prolonged or repeated courses of IV antibiotics; and use of IV antibiotics when oral antibiotics are adequate. An incorrect diagnosis of LD includes those patients with positive serologies without characteristic signs or symptoms of LD, or those with non-specific symptoms and no known exposure to ticks in an endemic area, or those without supporting serologic evidence.

The evidence generally does not support persistent B burgdorferi infection in patients with well-documented infection who have received recommended antibiotic therapy. Blinded, randomized controlled trials (RCTs) of extended antibiotic therapy versus placebo in such patients have shown no consistent differences in outcomes (summarized in the Table). Moreover, prolonged exposure to antibiotics carries a high risk of side
effects, including pseudomembranous colitis and the accumulation of ceftriaxone calcium salts in the gall bladder.

While morphologic variants of *B burgdorferi* have been thought to be related to persistent Lyme disease symptoms, a 2013 systematic review by Lantos et al found no evidence to support this. The reviewers found no pathogenic relationship between morphologic variants of *B burgdorferi* and persistent symptoms of Lyme disease. Additionally, no literature was identified that would support a role for treatment of *B burgdorferi* morphologic variants.

**Table. Summary of RCT of Prolonged Antibiotic Therapy in Patients With Well-Documented, Previously Treated Lyme Disease**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Patient Description</th>
<th>Experimental Treatment</th>
<th>Control Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klempner et al (2001)</td>
<td>78</td>
<td>(1) Positive for IgG Abs to <em>B burgdorferi</em>; persistent symptoms that interfered with patient function (2) Negative for IgG Abs to <em>B burgdorferi</em>; else, as above</td>
<td>IV ceftriaxone daily for 30 d, oral doxycycline for 60 d</td>
<td>IV and oral placebos</td>
<td>No significant difference in QOL outcomes for 1 and 2. Studies terminated after interim analysis indicated that it was highly unlikely that a significant difference in treatment efficacy would be observed.</td>
</tr>
<tr>
<td>Kaplan et al (2003)</td>
<td>129</td>
<td>Same trial as Klempner et al (2001)</td>
<td></td>
<td></td>
<td>Both treatment and control arms showed similar and not significantly different decreases in Medical Outcomes Study cognitive, pain, and role functioning scales; and improved mood as assessed with BDI and MMPI.</td>
</tr>
<tr>
<td>Krupp et al (2003)</td>
<td>55</td>
<td>Patients with persistent severe fatigue of duration ≥6 mo</td>
<td>IV ceftriaxone daily for 28 d</td>
<td>IV placebo</td>
<td>Ceftriaxone treatment arm showed no significant improvement in primary outcome of laboratory measure of persistent infection. Significant improvement in secondary outcome of disabling fatigue; no significant treatment effect on cognitive function; no difference in change in SF-36 scores. Patients in ceftriaxone group significantly more likely to correctly identify their treatment assignment.</td>
</tr>
<tr>
<td>Oksi et al (2007)</td>
<td>152</td>
<td>Consecutive patients treated with standard antibiotic regimen for 21 d</td>
<td>Amoxicillin twice daily for 100 d starting immediately after standard regimen</td>
<td>Placebo twice daily for 100 d starting immediately after standard regimen</td>
<td>Both treatment and control arms showed similar and not significantly different decreases in patient and investigator VAS outcomes (VAS evaluation of symptoms, range, 0-100; 0=no symptoms) at 12 mo. <em>B burgdorferi</em>-specific antibodies declined similarly in both groups over 12 mo.</td>
</tr>
<tr>
<td>Fallon et al (2007)</td>
<td>37</td>
<td>Patients with</td>
<td>IV ceftriaxone</td>
<td>IV placebo</td>
<td>Primary outcome of cognitive function</td>
</tr>
</tbody>
</table>
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(2008) documented objective memory impairment
daily for 70 d
across 6 domains similarly improved in both groups at week 24 and not significantly different between groups; improvement between groups marginally significantly different at week 12 (p=0.05). Exploratory subgroup analyses suggested significantly better improvement in ceftriaxone-treated patients with more severe baseline pain and physical functioning.

Cameron (2008) 86 Patients with symptoms of arthralgia, cardiac or neurologic involvement with or without fatigue after previous successful antibiotic treatment of Lyme disease; study conducted in a primary care internal medicine practice (52 assigned, 31 evaluable)
Oral amoxicillin 3 g daily for 3 mo (34 assigned, 17 evaluable)
Oral placebo daily for 3 mo
• 44% of enrolled patients not evaluable at 6 mo; 17 had poorer baseline QOL and were lost due to treatment failure
• SF-36 improvements for antibiotic vs placebo arm were significant (46% vs 18%, p=0.007), but text not clear if analysis of all or only evaluable patients
• SF-36 Physical Component Summary improvement not significantly different between treatment arms for evaluable patients (8.5 vs 7)
• SF-36 Mental Component Summary significantly improved in antibiotic arm for evaluable patients (14.4 vs 6.2, p=0.04)

BDI: Beck Depression Inventory; IgG: immunoglobulin G; IV: intravenous; MMPI: Minnesota Multiphasic Personality Inventory; QOL: quality of life; SF-36: 36-Item Short-Form Health Survey; VAS: visual analog scale.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Comparison of Ceftriaxone and Doxycycline for Treatment of Multiple Erythema Migrans</td>
<td>720</td>
<td>Oct 2015</td>
</tr>
<tr>
<td>NCT01163994</td>
<td>Study of Lyme Neuroborreliosis: Epidemiology, Manifestations, Diagnostics and Treatment</td>
<td>150</td>
<td>May 2016</td>
</tr>
<tr>
<td>NCT01207739</td>
<td>Persistent Lyme Empiric Antibiotic Study Europe. A Prospective,</td>
<td>280</td>
<td>Jun 2014</td>
</tr>
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Randomised Study Comparing Two Prolonged Oral Antibiotic Strategies After Initial Intravenous Ceftriaxone Therapy for Patients With Symptoms of Proven or Possible Persistent Lyme Disease

NCT: national clinical trial.

Summary of Evidence
The evidence for PCR–based detection of *B burgdorferi* in individuals who are suspected of having Lyme disease includes a review of the evidence with recommendations from the Centers for Disease Control and Prevention on tiered diagnostic testing. Relevant outcomes are test accuracy and validity, change in disease status, and morbid events. The optimum method of testing depends on the stage of the disease. Diagnostic testing may not be necessary when a diagnosis can be made clinically in patients with a recent tick bite or exposure and the presence of the characteristic rash of erythema migrans. When laboratory testing is needed, serologic testing using the 2-step ELISA followed by confirmation with Western blot is the recommended first approach. Polymerase chain reaction may be considered medically necessary as a second approach in patients with a short duration of neurologic symptoms (<14 days) or uncertainty in serologic testing. The evidence is considered sufficient to determine qualitatively that the technology results in an improvement in the net health outcome.

The evidence for other diagnostic tests in individuals who are suspected of having Lyme disease is limited. Relevant outcomes are test accuracy, change in disease status, and morbid events. Evidence for PCR-based testing in situations other than the approach described above is limited. There is little clinical utility in genotyping or phenotyping of *B burgdorferi*. Additional research is necessary to determine diagnostic and treatment utility of CXCL13. Other diagnostic testing approaches, such as C6 peptide ELISA, also warrant additional research. Evidence is insufficient to evaluate the effects of the technology on health outcomes.

The evidence for prolonged or repeated courses of antibiotic therapy in individuals with confirmed Lyme disease includes a number of RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and health status measures. Oral antibiotics usually are adequate for treatment of Lyme disease, but, in some cases, a 2- to 4-week course of IV antibiotics may be appropriate in cases of Lyme arthritis, carditis, or objective neurologic complications. Evidence from RCTs has not shown a benefit to prolonged (>4 weeks) or repeat courses of oral or IV antibiotics. The evidence is sufficient to determine quantitatively that the technology is unlikely to improve the net health outcome.

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06/21/2005 Medical Policy Committee review
07/15/2005 Managed Care Advisory Council approval
07/07/2006 Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
07/10/2007 Medical Director review
07/18/2007 Medical Policy Committee approval. Policy updated with literature search. Policy statements updated; uncomplicated cranial nerve palsy (e.g. Bell’s palsy) not considered a medically necessary indication for intravenous antibiotics.
08/06/2008 Medical Director review
08/20/2008 Medical Policy Committee approval. No change to coverage eligibility.
08/06/2009 Medical Policy Committee approval.
08/26/2009 Medical Policy Implementation Committee approval. No change to coverage eligibility.
08/05/2010 Medical Policy Committee review
08/10/2010 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2011 Medical Policy Implementation Committee approval
08/17/2011 Medical Policy Implementation Committee approval. Added a statement that determination of levels of the B lymphocyte chemokine CXCL13 for diagnosis or monitoring treatment is considered investigational.
08/02/2012 Medical Policy Committee review
08/15/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013 Coding revised
09/05/2013 Medical Policy Committee review
09/18/2013 Medical Policy Implementation Committee approval. Additional diagnostic testing added to the investigational section.
09/04/2014 Medical Policy Committee review
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/08/2016 Medical Policy Committee review
09/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date: 09/2017

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT), copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

Policy # 00173
Original Effective Date: 07/15/2005
Current Effective Date: 09/21/2016

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
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<tbody>
<tr>
<td>CPT</td>
<td>86617, 86618, 86619, 87475, 87476, 87477</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>A69.20-A69.29, A87.2, G04.81, G04.90-G04.91, G37.4, G50.9-G51.0, G50.19-G20.29, G53, G60.9, H47.091-H47.099, H49.00-H49.03, H49.10-H49.13, H49.20-H49.23, H93.3X1-H93.3X9, H94.00-H94.03, H94.10-H49.13, I51.89</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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