



Louisiana

Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

Policy # 00173

Original Effective Date: 07/15/2005

Current Effective Date: 12/20/2017

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 (LD) 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.

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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.

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.

Lyme Carditis

A single 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 (AV) block or a PR interval of >0.3sec.

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.

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.

When Services Are Considered Investigational

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

Diagnostic Testing

Based on review of available data, the Company considers repeat polymerase chain reaction (PCR)-based direct detection of *B. burgdorferi* in the following situations 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.

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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 “stand alone” C6 peptide ELISA or determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment to be **investigational**.*

Antibiotic Therapy

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, in the absence of objective clinical or laboratory evidence of Lyme disease (LD);
- 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

LD is a multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi* and transmitted by the bite of an infected *Ixodes scapularis* (northeastern region) or *Ixodes pacificus* (Pacific coast, most often in Northern California) tick. The disease is characterized by stages, beginning with localized infection of the skin (erythema migrans), followed by acute dissemination, and then late dissemination to many sites. Manifestations of the early disseminated disease may include lymphocytic meningitis, facial palsy, painful radiculoneuritis, AV 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 AV block. The following

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paragraphs describe the various manifestations of LD, therapies, and the various laboratory tests used to support the diagnosis of LD.

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 patient has 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. Usual treatment consists of 2 weeks of either oral (ambulatory setting) or IV (hospitalized patients) antibiotics.

Cranial neuritis, most frequently Bell palsy, may present early in the course of disseminated LD, occasionally before the development of antibodies, such that a LD etiology may be difficult to rule in or out. While Bell 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, magnetic resonance imaging, or CSF. Also, the symptoms are nonspecific and overlap with fibromyalgia and chronic fatigue syndrome. Thus the diagnosis of Lyme encephalopathy may be difficult and may best be made with a mental status exam or neuropsychological testing. Treatment with IV antibiotics is 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. CSF examination reveals pleocytosis and elevated protein. Selective synthesis of anti-spirochetal antibodies can also be identified. A course of IV antibiotics with 2 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 or nerve conduction velocity abnormalities. CSF abnormalities are usually seen only in those patients with a coexistent encephalopathy.

Lyme Carditis

Lyme carditis may appear during the early disseminated stage of the disease; symptoms include AV block, tachyarrhythmias, and myopericarditis. Antibiotics are typically given, although no evidence has demonstrated hastened resolution of symptoms. Both oral and IV regimens have been advocated. IV regimens are used in patients with high degree AV block or a PR interval on the electrocardiogram more than 0.3 seconds. Patients with milder forms of carditis may be treated with oral antibiotics.

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Lyme Arthritis

Lyme arthritis is a late manifestation of infection and is characterized by an elevated immunoglobulin G (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 involvement, requiring IV antibiotic treatment. In the small subset of patients who 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 more 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 with LD, both of these conditions lack joint inflammation, have normal neurologic test results, or have test results suggesting anxiety or depression. Neither fibromyalgia nor chronic fatigue syndrome has been shown to respond to antibiotic therapy.

Diagnostic Testing

Overview

The optimum method of testing for LD 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. While diagnosis of LD is generally based on the clinical picture and demonstration of specific antibodies (see next), PCR-based technology can detect the spirochete in the CNS 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, 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.

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. PCR may be clinically useful as a second approach in patients with a short duration of neurologic symptoms (<14 days) during the window between exposure and the emergence of detectable levels of antibodies in the CSF. PCR-based detection is typically not performed in the urine due to the variable presence of endogenous polymerase inhibitors that affect test sensitivity.

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 immunoglobulin M (IgM)

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response characteristic of acute infection peaks between the third and the 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% to 10%. Thus, as with any laboratory test, interpretation of serologic tests requires close correlation with the patient's 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 to establish the diagnosis of LD. Inevitably, in this setting of repeat testing, 1 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 recommend a 2-tiered method for the serologic diagnosis of LD: (1) ELISA or immunofluorescence assay, followed by (2) a confirmatory Western blot (including both IgM and IgG when signs or symptoms have been present ≤ 30 days; IgG only if symptoms have been present > 30 days). A negative ELISA or immunofluorescence assay may be followed by a later (e.g., in 4 to 6 weeks) convalescent serum test when symptoms have been present 30 days or less.

ELISA for B. burgdorferi Antibodies

This ELISA test is a screening serologic test for LD. ELISA tests are available to detect IgM or IgG antibodies or 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 a Western blot. Also, results must be correlated with the clinical picture.

(Western) Immunoblot

This immunoblot test is used to confirm the serologic diagnosis of LD in patients with positive or indeterminate ELISA tests. In contrast with the standard ELISA test, the immunoblot investigates the specific antibody response to the different antigens of *B. burgdorferi*. Typically, several clinically significant antigens are tested. According to 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 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. U.S. criteria for interpreting immunoblot results differ from those in Europe due to differences in prevalent *Borrelia* species causing disease.

Polymerase Chain Reaction

In contrast to the previously discussed serologic tests, which indirectly assess prior or present exposure to *B. burgdorferi*, PCR directly tests for the presence of the spirochete. Because PCR technology involves amplification of DNA from a portion of *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

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serology are not definitive for diagnosis. Also, 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 who may not be indicated with a recent history of tick bite or exposure) and for synovial tissue (and synovial fluid, to a lesser extent) from patients with Lyme arthritis. CSF may be positive by PCR during the first 2 weeks of infection, but after that the detection rate is low. PCR is not recommended for urine or blood specimens. However, PCR-based direct detection of *B. burgdorferi* in the blood may be useful for documenting Lyme carditis when results of serologic studies are equivocal.

Borrelia PCR also provides information on which of the 3 major species pathogenic for humans has been found in the specimen tested (genotyping).

T-Cell Proliferative Assay

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

Evaluation of CSF

Aside from the standard evaluation of CSF for pleocytosis, protein levels, and glucose levels, various tests are available to determine whether anti-*B. burgdorferi* antibodies are being selectively produced within the CNS. Techniques include a variety of immunoassays. For example, intrathecal antibody production can be detected by the CSF/serum index of *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 *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 2 weeks of infection.

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.

Treatment of Lyme Disease

As previously noted, treatment with IV antibiotics may be 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 or penicillin. No data have suggested 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. Also, 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.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration

The FDA has cleared multiple enzyme immunoassay (EIA), immunofluorescent assay and Western Blot IgG and IgM tests through the 510(k) process. There are also commercially available laboratory- developed tests for serologic testing for LD. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

SUSPECTED LYME DISEASE

Analysis of Borrelia Burgdorferi Genotype

PCR-based technology has been used as 1 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 4 distinct species and genomic groups. Of these, the following have been isolated from patients with LD: *B. burgdorferi sensu stricto*, *B. garinii*, *B. afzelii*, and *B. bavariensis*. The prevalence of these 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 United States, *B. burgdorferi sensu stricto* and *B. mayonii* are the only human pathogenic species, but in Europe, all 3 species cause infection. In 2007, *B. spielmanii* was found in a small number of European patients; accordingly, criteria for interpreting immunoblot results differ in Europe than in the United States.

Section Summary: Analysis of Borrelia Burgdorferi Genotype

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.

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Chemokine CXCL13 and C6 Peptide

CXCL13 is a B-lymphocyte chemoattractant that has been reported to be elevated in acute neuroborreliosis, making it a potential marker for successful treatment. However, data are limited.

Other diagnostic testing strategies, such as single step EIA using the C6 peptide, have not demonstrated improvements in specificity over the 2-tiered testing approach. Branda et al (2011) reported on the use of whole-cell sonicate EIA (ELISA) followed by C6 EIA, and found the specificity and positive predictive values were comparable with the 2-tiered ELISA–Western blot approach (99.5% vs 98.4%, and 70% vs 66%, both respectively). Lipsett et al (2016) evaluated C6 EIA in 944 children of whom 114 (12%) had LD. They found stand-alone C6 EIA testing had lower specificity than 2-tiered testing (94.2% vs 98.8%); specificity was increased to 98.6% with a supplemental immunoblot. A 2016 systematic review assessing diagnosis and treatment of LD also concluded that “stand-alone” C6 testing is not recommended over the 2-tiered approach due to slightly lower specificity.

Section Summary: Chemokine CXCL13 and C6 Peptide

Data are limited on the determination of CXCL 13 levels in patients suspected of having LD. Additional research is necessary to determine diagnostic and treatment utility. Stand-alone C6 testing is not recommended over the 2-tier approach.

CONFIRMED LYME DISEASE

Role of Intravenous or Prolonged Oral Antibiotic Therapy

The evidence does not support persistent *B. burgdorferi* infection in patients with well-documented infection who have received recommended antibiotic therapy. Blinded, RCTs of extended antibiotic therapy vs placebo in such patients have shown no consistent differences in outcomes (summarized in Table 1).

While morphologic variants of *B. burgdorferi* are thought to be related to persistent LD symptoms, a 2014 systematic review by Lantos et al found no evidence to support this. Reviewers found no pathogenic relation between morphologic variants of *B. burgdorferi* and persistent symptoms of LD. Additionally, no literature was identified that would support a role for treatment of *B. burgdorferi* morphologic variants.

Section Summary: Role of Intravenous or Prolonged Oral Antibiotic Therapy

Oral antibiotics usually are adequate for treatment of LD, though in some persistent cases, a 2- to 4-week course of IV antibiotics may be appropriate. Evidence from RCTs has not shown a benefit to prolonged (>4 weeks) or repeat courses of oral or IV antibiotics.

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Table 1. Summary of Randomized Controlled Trials of Prolonged Antibiotic Therapy in Patients With Well-Documented, Previously Treated Lyme Disease

Study (Year)	N	Patient Description	Experimental Treatment	Control Treatm	Results
Klempner et al (2001)	78	<ul style="list-style-type: none"> Positive for IgG to <i>B. burgdorferi</i>; persistent symptoms interfered with patient function Negative for IgG to <i>B. burgdorferi</i>; else, as above 	<ul style="list-style-type: none"> IV ceftriaxone daily for 30 d oral doxycycline for 60 d 	IV and oral placebo	No significant difference in QOL outcomes for either patient group. Studies terminated after interim analyses indicated it was highly unlikely that a significant difference in treatment efficacy would be observed.
Kaplan et al (2003)	129	Same trial as Klempner et al (2001)			Both treatment and control arms showed similar and not significantly different decreases in SF-36 cognitive, pain, and role functioning scales, and improved mood as assessed with BDI and MMPI
Krupp et al (2003)	55	Patients with persistent severe fatigue ≥ 6 mo	IV ceftriaxone daily for 28 d	IV placebo	Ceftriaxone treatment arm showed no significant improvement in primary outcome (laboratory measure of persistent infection). Significant improvement in secondary outcome (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.
Oksi et al (2007)	152	Consecutive patients treated with standard antibiotic regimen for 21 d	Amoxicillin twice daily for 100 d starting immediately after standard regimen	Placebo twice daily for 100 d starting immediately after standard regimen	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. <i>B. burgdorferi</i> -specific antibodies declined similarly in both groups over 12 mo.
Fallon et al (2008)	37	Patients with documented objective memory impairment	IV ceftriaxone daily for 70 d	IV placebo daily for 70 d	The primary outcome (cognitive function across 6 domains) similarly improved in both groups at week 24 and did not differ significantly 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	Oral amoxicillin 3 g daily for 3 mo (34 assigned, evaluable)	Oral placebo daily for 3 mo	<ul style="list-style-type: none"> 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

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Study (Year)	N	Patient Description	Experimental Treatment	Control Treatm	Results
		antibiotic treatment of Lyme disease; study conducted in a primary care internal medicine practice (52 assigned, 31 evaluable)			18%, p=0.007), but not clear whether analysis included all or only evaluable patients <ul style="list-style-type: none"> SF-36 PCS improvement did not differ significantly between treatment arms for evaluable patients (8.5 vs 7) SF-36 MCS significantly improved in antibiotic arm for evaluable patients (14.4 vs 6.2, p=0.04)
Berende et al (2016)	280	Patients with persistent Lyme disease symptoms given IV ceftriaxone for 2 wk	Doxycycline or clarithromycin/hydroxyl-chloroquine for 12 wk	Placebo	<ul style="list-style-type: none"> SF-36 PCS did not differ across 3 study groups Adverse event rates similar across 3 study groups 4 serious ceftriaxone-related adverse events

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

SUMMARY OF EVIDENCE

Suspected Lyme Disease

For individuals who are suspected of having LD who receive genotyping or phenotyping of *B. burgdorferi* subspecies or are tested for determination of CXCL13 levels or C6 peptide assay, the evidence is limited. Relevant outcomes are test accuracy, change in disease status, and morbid events. PCR-based testing for *B. burgdorferi* genospecies is feasible. However, no evidence was identified that knowledge of the *B. burgdorferi* genotype or phenotype could be used to improve patient management and outcomes. Additional research is also needed to determine the diagnostic utility of CXCL13 and C6 peptide levels. The evidence is insufficient to determine the effects of the technology on health outcomes.

Confirmed Lyme Disease

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

It is well established that the optimum method of testing for LD depends on the stage of disease. Guidelines from the CDC and other sources have support policy statements related to a tiered diagnostic testing strategy. 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

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Louisiana

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Policy # 00173

Original Effective Date: 07/15/2005

Current Effective Date: 12/20/2017

laboratory testing is indicated, 2-tiered serologic testing is recommended. PCR may be clinically useful as a second approach in patients with a short duration of neurologic symptoms (<14 days).

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Louisiana

Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

Policy # 00173

Original Effective Date: 07/15/2005

Current Effective Date: 12/20/2017

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Policy History

Original Effective Date: 07/15/2005

Current Effective Date: 12/20/2017

- | | |
|------------|---|
| 06/07/2005 | Medical Director review |
| 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 Committee review |
| 08/17/2011 | Medical Policy Implementation Committee approval. Added a statement that determination of levels of the B lymphocyte chemoattractant 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 |

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Policy # 00173

Original Effective Date: 07/15/2005

Current Effective Date: 12/20/2017

09/18/2013 Medical Policy Implementation Committee approval. Additional diagnostic testing added to the investigational section.

09/04/2014 Medical Policy Committee review

09/17/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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

12/07/2017 Medical Policy Committee review

12/20/2017 Medical Policy Implementation Committee approval. "Stand-alone" added to the investigational statement on C6 peptide ELISA. Coverage eligibility unchanged.

04/01/2018 Coding update

Next Scheduled Review Date: 12/2018

Coding

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Code Type	Code
CPT	86617, 86618, 86619, 87475, 87476, 87477 Codes added eff 4/1/18: 0041U, 0042U, 0043U, 0044U
HCPCS	No codes
ICD-10 Diagnosis	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 I44.30 I51.89

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- 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:
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 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

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- 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.

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