Medical Policy

BlueCross BlueShield of Kansas
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Title: Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

Professional
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DESCRIPTION

Lyme disease is a multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi* and transmitted by the bite of an infected ixodid tick. The disease is characterized by stages, beginning with localized infection of the skin (erythema migrans), followed by dissemination to many sites. Oral antibiotics usually are adequate for treatment of Lyme disease, but in some cases, intravenous antibiotics may be appropriate. Diagnostic testing for Lyme disease is challenging and can lead to overdiagnosis and overtreatment.

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 Lyme disease can be adequately treated with oral antibiotics, intravenous (IV) antibiotics are indicated in some patients with neurologic involvement or atrioventricular heart block. However, overdiagnosis and overtreatment of Lyme disease 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 Lyme disease 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 Lyme disease that may prompt therapy with IV antibiotics and the various laboratory tests that are used to support the diagnosis of Lyme disease.

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 cerebrospinal fluid (CSF) is indispensable for the diagnosis of Lyme meningitis. If the patient has Lyme disease, 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 Lyme disease, occasionally prior to the development of antibodies, such that a Lyme disease etiology may be difficult to rule in or out. 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. CSF examination reveals a pleocytosis and an elevation in protein. Selective synthesis of anti-spirochetal antibodies 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 Lyme disease 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. CSF 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 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 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 central nervous system (CNS) 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 Lyme disease. 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 Lyme disease, both of the above 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.

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) 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 Lyme disease may persist for months or years. Thus detection of IgG antibodies only indicates exposure, either past or present. In Lyme disease 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 patient's signs and symptoms. For example, patients with vague symptoms of Lyme disease, chronic fatigue syndrome, or fibromyalgia may undergo multiple serologic tests over many weeks to months in an effort to establish the diagnosis of Lyme disease. Inevitably, in this setting of repeat testing, one enzyme-linked immunosorbent assay (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 Centers for Disease Control and Prevention (CDC) recommend a 2-step method for the serologic diagnosis of Lyme disease:

1. Enzyme-Linked Immunosorbent Assay (ELISA) for *Borrelia burgdorferi* Antibodies
   This test is a screening serologic test for Lyme disease. ELISA 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 Lyme disease. All of these tests must be confirmed with an immunoblot test. In addition, results must be correlated with the clinical picture.

2. (Western) Immunoblot
   This test is used to confirm the serologic diagnosis of Lyme disease in patients with positive or indeterminate ELISA tests. In contrast to 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 the CDC criteria were developed for surveillance, they are conservative and may miss true Lyme disease 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 *Borrelia* species causing disease.

Other tests include:

Polymerase Chain Reaction (PCR)

In contrast to the above 2 serologic tests, which only 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 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. CSF may be positive by PCR during the first 2 weeks of infection, but thereafter 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; they are difficult to perform and standardize, and their sensitivity is not well-characterized.

Evaluation of Cerebrospinal Fluid (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 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 Lyme disease. 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.

POLICY

Treatment of Lyme disease consists of oral antibiotics, except for the following indications:

A. A 2- to 4-week course of IV antibiotic therapy may be considered **medically necessary** in patients with neuroborreliosis with objective neurologic complications of documented Lyme disease (see the following for methods of documentation).

Objective neurologic findings include:
- Lymphocytic meningitis with documented cerebrospinal fluid (CSF) abnormalities
- Cranial neuropathy, other than uncomplicated cranial nerve palsy, with documented CSF abnormalities
- Encephalitis or encephalomyelitis with documented CSF abnormalities
- Radiculopathy
- 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 CSF abnormalities is required for suspected CNS infection, as indicated above.

Serologic documentation of infection requires:
- Positive or indeterminate enzyme-linked immunosorbent assay (ELISA), AND
- Positive immunoblot blot by CDC criteria.

Documented CSF abnormalities include **ALL** of the following:
- Pleocytosis;
- Evidence of intrathecal production of *Borrelia burgdorferi* antibodies in CSF; and
- Increased protein levels.

Polymerase chain reaction (PCR)-based direct detection of *B. burgdorferi* in CSF samples may be considered **medically necessary** 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.

B. A single 2- to 4-week course of IV antibiotics may be considered **medically necessary** in patients with Lyme carditis, as evidenced by positive serologic findings (defined above) and associated with a high degree of atrioventricular block or a PR interval of greater than 0.3 second. Documentation of Lyme carditis may include PCR-based direct detection of *B. burgdorferi* in the blood when results of serologic studies are equivocal.

C. A single 2- to 4-week course of IV antibiotic therapy may be considered **medically necessary** in the small subset of patients with well-documented Lyme arthritis who have such severe arthritis that it requires the rapid response associated with IV antibiotics. Documentation of Lyme arthritis may include PCR-based direct detection of *B. burgdorferi* in the synovial tissue or fluid when results of serologic studies are equivocal.

D. Intravenous antibiotic therapy is considered **not medically necessary** in the following situations:
   1. Patients with symptoms consistent with chronic fatigue syndrome or fibromyalgia, in the absence of objective clinical or laboratory evidence for Lyme disease;
   2. Patients with seronegative Lyme disease in the absence of CSF antibodies;
   3. Initial therapy in patients with Lyme arthritis without coexisting neurologic symptoms;
   4. Cranial nerve palsy (e.g., Bell's palsy) without clinical evidence of meningitis;
   5. Antibiotic-refractory Lyme arthritis (unresponsive to 2 courses of oral antibiotics or to 1 course of oral and 1 course of intravenous antibiotic therapy);
   6. Patients with vague systemic symptoms without supporting serologic or CSF studies;
   7. Patients with a positive ELISA test, unconfirmed by an immunoblot or Western blot test (see definition above);
   8. Patients with an isolated positive serologic test in the setting of multiple negative serologic studies;
   9. Patients with chronic (≥6 months) subjective symptoms ("post-Lyme syndrome") after receiving recommended treatment regimens for documented Lyme disease.

E. Repeat or prolonged courses (e.g., greater than 4 weeks) of IV antibiotic therapy are considered **not medically necessary**.

F. Repeat PCR-based direct detection of *B. burgdorferi* is considered **experimental / investigational** in the following situations:
   1. As a justification for continuation of IV antibiotics beyond 1 month in patients with persistent symptoms
   2. As a technique to follow therapeutic response

G. PCR-based direct detection of *B. burgdorferi* in urine samples is considered **experimental / investigational** in all clinical situations.

H. Genotyping or phenotyping of *B. burgdorferi* is considered **experimental / investigational**.

I. Other diagnostic testing is considered **experimental / investigational** including but not limited to C6 peptide ELISA or determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment.

RATIONALE

This policy was originally created in 1998 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period of October 2011 through July 2012. The following is a summary of the key literature to date.

Direct Detection of Borrelia burgdorferi with Polymerase Chain Reaction (PCR) Technology
While diagnosis of Lyme disease is generally based on the clinical picture and demonstration of specific antibodies, PCR-based technology can detect the spirochete in the central nervous system (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. (1, 2) 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. (3) However, it should be noted that that the test cannot distinguish between live and dead organisms. PCR-based 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 *Borreliaburgdorferi.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 Lyme disease: *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. (4) 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. (5)

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. (2, 6) 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). (6) 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 (IV) Antibiotics

A diagnosis of Lyme disease 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 Lyme disease is common. (7-9) Intravenous antibiotic therapy in patients with presumed Lyme disease 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 Lyme disease includes those patients with positive serologies without characteristic signs or symptoms of Lyme disease, 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. (10) Blinded, randomized controlled trials 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. (11)

Table. Summary of randomized, controlled trials of prolonged antibiotic therapy in patients with well-documented, previously treated Lyme disease

Study	N	Patient description	Experimental treatment	Control treatment	Results
Klempner et al. 2001 (12)	78 51	1) Positive for IgG Abs to *B. burgdorferi*; persistent symptoms that interfered with patient function 2) Negative for IgG Abs to *B. burgdorferi*; else, as above	IV ceftriaxone daily for 30 days, oral doxycycline for 60 days	IV and oral placebos	No significant difference in quality of life 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
Kaplan et al. 2003 (13)	129	Same trial as Klempner et al. 2001 (12)			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 the Beck Depression Inventory and Minnesota Multiphasic Personality Inventory

Study	N	Patient description	Experimental treatment	Control treatment	Results
Krupp et al. 2003 (14)	55	Patients with persistent severe fatigue of duration 6 months or longer	IV ceftriaxone daily for 28 days	IV placebo	Ceftriaxone treatment arm showed no significant improvement in primary outcome of laboratory measure of persistent infection Significant improvement in the secondary outcome of disabling fatigue; no significant treatment effect on cognitive function; no difference in change in SF-36 scores Patients in ceftriaxone group were significantly more likely to correctly identify their treatment assignment.
Oksi et al. 2007 (15)	152	Consecutive patients treated with standard antibiotic regimen for 21 days	Amoxicillin twice daily for 100 days starting immediately after standard regimen	Placebo twice daily for 100 days starting immediately after standard regimen	Both treatment and control arms showed similar and not significantly different decreases in patient and investigator visual analogue scale (VAS) outcomes (VAS evaluation of symptoms, range 0-100, 0=no symptoms) at 12 mos. *B. burgdorferi*-specific antibodies declined similarly in both groups over 12 mos.
Fallon et al. 2008 (16)	37	Patients with documented objective memory impairment	IV ceftriaxone daily for 70 days	IV placebo daily for 70 days	Primary outcome of cognitive function across 6 domains was similarly improved in both groups at week 24, and was not significantly different between groups; improvement between groups was 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 (17)	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 gm daily for 3 months (34 assigned, 17 evaluable)	Oral placebo daily for 3 months	--44% of enrolled patients not evaluable at 6 months; 17 of these had poorer baseline quality of life 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 improvement not significantly different between treatment arms for evaluable patients (8.5 vs. 7); --SF-36 mental component significantly improved in antibiotic arm for evaluable patients (14.4 vs. 6.2, p=0.04)

Ongoing clinical trials

A search of online site ClinicalTrials.gov in August 2012 identified no randomized controlled trials that addressed prolonged or repeated courses of intravenous antibiotics. Two randomized controlled trials were identified that will compare the effectiveness of oral doxycycline to intravenous ceftriaxone. One study will focus on patients with Lyme neuroborreliosis (NCT01635530), and the other will focus on patients with multiple erythema migrans (NCT01163994). Another randomized controlled trial, Persistent Lyme Empiric Antibiotic Study Europe (PLEASE), will compare outcomes after 12 weeks of treatment with 2 oral antibiotics (doxycycline or clarithromycin and hydroxychloroquine) or placebo after initial intravenous ceftriaxone. (NCT01207739) This study is expected to be completed in September 2013.

Summary

Lyme disease is a multisystem inflammatory disease caused by *Borrelia burgdorferi* and transmitted by the bite of an infected ixodid tick. Oral antibiotics usually are adequate for treatment of Lyme disease, but in some cases, a 2-4-week course of intravenous (IV) antibiotics may be appropriate such as in cases of Lyme arthritis, carditis or objective neurologic complications. Evidence has not shown a benefit to prolonged (greater than 4 weeks) or repeat courses of IV antibiotics. Therefore, repeat or prolonged courses of antibiotic therapy are considered not medically necessary.

Diagnostic testing for Lyme disease is challenging and can potentially lead to overdiagnosis and overtreatment. 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 studies are needed, serologic testing using the 2-step ELISA followed by Western blot is the recommended first approach. Polymerase chain reaction (PCR), 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. Other uses for PCR-based testing are considered investigational. Genotyping or phenotyping of *B burgdorferi* is considered investigational. Additional research is necessary to determine diagnostic and treatment utility of the CXCL13, and its use is considered investigational. Other diagnostic testing approaches, such as C6 peptide, also warrant additional research and therefore, are considered investigational.

Practice Guidelines and Position Statements

In 1993, the American College of Rheumatology published a position paper on IV antibiotic treatment for Lyme disease, which concluded that “empiric treatment of patients with nonspecific chronic fatigue or myalgia on the basis of positive serologic results alone will result in many more instances of antibiotic toxicity than cures of atypically symptomatic true Lyme disease...In patients whose only evidence for Lyme disease is a positive immunologic test, the risks for empiric IV antibiotic treatment outweigh the benefits....” (9) Other studies have also supported the use of oral, not IV, antibiotics in patients with Lyme disease without neurologic involvement. (18-20)

Practice guidelines regarding the treatment of Lyme disease and including discussion of supportive evidence have been issued by the Infectious Diseases Society of America (IDSA). (21) The IDSA also endorsed the American Academy of Neurology evidence-based practice parameter for the treatment of nervous system Lyme disease. (10) The IDSA guidelines recommend IV antibiotics only in the following situations (Note: none of the recommendations suggest longer than a 1-month course of IV antibiotics):

- Early neurologic disease
  - Meningitis or radiculopathy: 14–28 days
- Cardiac disease
  - Acute onset of varying degrees of intermittent atrioventricular heart block, sometimes in association with clinical evidence of myopericarditis: 14–21 days
- Late disease
  - Persistent or recurrent arthritis after initial oral regimen: 14–28 days (a second, 4-week oral regimen may also be used)
  - CNS or peripheral nervous system disease: 14–28 days

In the particular case of cranial nerve palsy associated with Lyme disease (most commonly Bell's palsy, also known as 7th nerve palsy) and without clinical evidence of meningitis, the evidence indicates that oral antibiotic therapy is satisfactory. (10, 21) Cranial nerve palsy may, in fact, resolve without treatment, but treatment should be administered to avoid late complications of Lyme disease.

In addition, guidelines recommend symptomatic treatment for symptoms that persist after appropriate antibiotic therapy. For example, in a small number of patients with known prior infection, arthritis may persist despite negative *B burgdorferi* DNA by PCR in synovial fluid or tissue. Such persistent arthritis is termed "antibiotic-refractory Lyme arthritis," defined as "persistent synovitis for at least 2 months after completion of a course of intravenous ceftriaxone (or after completion of two 4-week courses of an oral antibiotic for patients unable to tolerate cephalosporins), in conjunction with negative results of PCR." (21) Symptomatic treatment, rather than additional antibiotic treatment, is recommended. (21)

In November 2006, the Connecticut Attorney General initiated an antitrust investigation to determine whether the Infectious Diseases Society of America violated antitrust laws in the promulgation of their 2006 Lyme disease guidelines for assessing and treating Lyme disease. The investigation ended with an agreement under which the guidelines remained in effect while the Society convened a Review Panel to determine whether or not the 2006 guidelines were based on sound medical/scientific evidence or required revision. The final report of the Review Panel details the methodology, results, and conclusions of the review. (22) According to the report, "After multiple meetings, a public hearing, and extensive review of research and other information, the Review Panel concluded that the recommendations contained in the 2006 guidelines were medically and scientifically justified on the basis of all of the available evidence and that no changes to the guidelines were necessary." The 2006 guidelines were reaffirmed in 2010.

The European Federation of Neurological Societies (EFNS) guidelines on Lyme neuroborreliosis are similar to the IDSA guidelines and recommend a 14-day course of oral or intravenous antibiotics in definite or possible acute Lyme neuroborreliosis. (23) In patients with late Lyme neuroborreliosis, a 3-week course of intravenous antibiotics is recommended. The EFNS guidelines indicate antibiotic use for post-Lyme disease syndrome has shown no effect.

Similar recommendations can be found in the British Infection Association's (BIA) position statement on Lyme disease, which indicates intravenous antibiotics may be appropriate in Lyme carditis, meningitis, or arthritis for periods of 14 to 21 days. (24) Late neuroborreliosis can be treated with intravenous antibiotics for 14-28 days. The BIA's position statement also notes the use of long-term antibiotics can be harmful.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

86617	Antibody; *Borrelia burgdorferi* (Lyme disease) confirmatory test (e.g., Western blot or immunoblot)
87475	Infectious agent detection by nucleic acid (DNA or RNA); *Borrelia burgdorferi*, direct probe technique
87476	Infectious agent detection by nucleic acid (DNA or RNA); *Borrelia burgdorferi,* amplified probe technique (describes PCR technique)
87477	Infectious agent detection by nucleic acid (DNA or RNA); *Borrelia burgodorferi;* quantification
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96367	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)
96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure)
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
96375	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of a new substance/drug (List separately in addition to code for primary procedure)
96376	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility (List separately in addition to code for primary procedure)

- Three different CPT codes describe direct detection of *B. burgdorferi*: direct probe (87475), amplified probe technique (87476), and quantification (87477). When these codes were introduced in 1998, for the sake of consistency, the same grouping of 3 codes was used for a wide variety of different organisms. However, only the amplified probe technique (87476) is used clinically for the detection of *B. burgdorferi*. The direct probe technique (87475) is not clinically useful due to the small numbers of organisms present. The quantification technique (87477) has no clinical role at this time since treatment decisions are not based on the quantification of organisms present. Therefore, codes 87475 and 87477 would be considered experimental / investigational.

ICD-9 Diagnoses

049.0	Lymphocytic meningitis
088.81	Lyme disease
323.81	Other causes of encephalitis
323.9	Unspecified cause of encephalitis
350.9	Trigeminal nerve disorder, unspecified
351.0	Bell's palsy
351.9	Facial nerve disorder, unspecified
352.0	Disorders of olfactory (1st) cranial nerve
352.2–352.6	Disorders of other cranial nerves, code range
352.9	Unspecified disorder of cranial nerves
356.9	Unspecified hereditary and idiopathic peripheral neuropathy (includes polyneuropathy)
377.49	Other disorders of optic nerve
378.51–378.54	Paralytic strabismus code range
388.5	Disorders of acoustic nerve
426.10	Atrioventricular block, unspecified
429.89	Other ill-defined heart diseases (includes Lyme carditis)

ICD-10 Diagnoses (Effective October 1, 2014)

A69.20	Lyme disease, unspecified
A69.21	Meningitis due to Lyme disease
A69.22	Other neurologic disorders in Lyme disease
A69.23	Arthritis due to Lyme disease
A69.29	Other conditions associated with Lyme disease

REVISIONS

04-04-2011	Policy added to the bcbsks.com web site.
04-12-2012	Description section updated
	In Policy section: ▪ Added to C 1 "in the absence of objective clinical or laboratory evidence for Lyme disease" to read "Patients with symptoms consistent with chronic fatigue syndrome or fibromyalgia, in the absence of objective clinical or laboratory evidence for Lyme disease;" ▪ Revised in C 9 ">" to "≥" to read, "Patients with chronic (≥6 months) subjective symptoms…" ▪ Revised in H "Determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment is considered experimental / investigational." to "Other diagnostic testing is considered experimental / investigational including but not limited to C6 peptide ELISA or determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment."
	Rationale section updated
	In Coding section: ▪ Updated nomenclature for CPT codes: 86617, 87475, 87476, 87477, 96367
	References updated

12-07-2012	Description section updated
	Rationale section updated
	References updated
02-28-2014	In Coding Section: ▪ ICD-10 Diagnoses codes added

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