BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

Policy #: 359
Category: Pharmacology

Latest Review Date: February 2021
Policy Grade: Effective October 26, 2015: Active policy but no longer scheduled for regular literature reviews and updates.

BACKGROUND:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. Safe and effective;
2. Not experimental or investigational*;
3. Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:
   - Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;
   - Furnished in a setting appropriate to the patient's medical needs and condition;
   - Ordered and furnished by qualified personnel;
   - One that meets, but does not exceed, the patient's medical need; and
   - At least as beneficial as an existing and available medically appropriate alternative.

*Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare** for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).

POLICY:

Effective for dates of service on or after February 19, 2021:

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

Blue Advantage will treat an **initial 2- to 4-week course of IV antibiotic therapy** as a **covered benefit** for members 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
- Encephalitis or encephalomyelitis with documented CSF abnormalities
- Cranial neuropathy, other than uncomplicated cranial nerve palsy, with documented CSF abnormalities
- Radiculopathy
- Polyneuropathy

Lyme carditis is suspected based on presence of one or more of the following:

- A high degree of artrioventicular block
- A PR interval of greater than 0.3 seconds
- Myopericarditis

Lyme arthritis with persistent, recurrent, or worsening joint swelling that has not resolved after a recommended course of oral antibiotic therapy.

Blue Advantage will treat **one repeat 2- to 4- week course of IV antibiotic therapy** as a covered benefit when all of the following criteria are met:

- Criteria for initial course of IV antibiotic therapy are met
- Laboratory values confirming Lyme disease have been obtained within the past 3 months
- The patient has completed the initial course of IV antibiotic therapy
- One or more of the following are met:
  - The initial infection has relapsed
  - Organ damage as a result of Lyme disease has progressed
  - Finding of a new focus or type of organ damage

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 central nervous system (CNS) infection, as indicated below.

Serologic documentation of infection requires:

- Positive or indeterminate enzyme immunoassay (EIA or ELISA) followed by either of the following:

- Positive immunoblot blot by Centers for Disease Control and Prevention (CDC) criteria; or
- Second positive enzyme immunoassay (EIA or ELISA)

Documented CSF abnormalities include ALL of the following:

- Pleocytosis;
- Evidence of intrathecal production of Borrelia burgdorferi antibodies in CSF; and
- Increased protein levels.

Blue Advantage will treat **polymerase chain reaction (PCR)-based direct detection of B. burgdorferi (by direct or amplified probe) in CSF samples** as a **covered benefit** and may replace serologic documentation of infection in members with a short duration of neurologic symptoms (<14 days) during the window between exposure and production of detectable antibodies.

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

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.

Intravenous antibiotic therapy for Lyme disease is **considered not medically necessary** in the following situations:

- Members with symptoms consistent with chronic fatigue syndrome or fibromyalgia, in the absence of objective clinical or laboratory evidence for Lyme disease;
- Members with seronegative LD in the absence of 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 antibiotic therapy);
- Members with vague systemic symptoms without supporting serologic or CSF studies;
- Members with a positive ELISA test, unconfirmed by an immunoblot or Western blot test (see definition above);
- Members with an isolated positive serologic test in the setting of multiple negative serologic studies;
- Members with chronic (> 6 months) subjective symptoms ("post-Lyme syndrome") after receiving recommended treatment regimens for documented LD.

Blue Advantage will treat **repeat PCR-based direct detection of B. burgdorferi** (by direct or amplified probe) as a **non-covered benefit** in the following situations:

- As a justification for continuation of IV antibiotics beyond 1 month in patients with persistent symptoms
- As a technique to follow therapeutic response

Blue Advantage will treat **PCR-based direct detection of B. burgdorferi in urine samples** as a **non-covered benefit and investigational** in all clinical situations.

Blue Advantage will treat **genotyping or phenotyping of B. burgdorferi** as a **non-covered benefit** and **investigational**.

Blue Advantage will treat **determination of levels of the B lymphocyte chemoattractant CXCL 13 for diagnosis or monitoring treatment** as a **non-covered benefit** and as investigational.

Blue Advantage will treat **other diagnostic testing including but not limited to "stand alone" C6 peptide ELISA** as a **non-covered benefit** and **investigational**.

Effective for dates of service March 2, 2018, through February 18, 2021:
Treatment of Lyme disease (LD) consists of oral antibiotics, except for the following indications:

Blue Advantage will treat a **2- to 4-week course of IV antibiotic therapy** as a **covered benefit** for **members with neuroborreliosis with objective neurologic complications of documented LD** (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 central nervous system (CNS) infection, as indicated above.

Serologic documentation of infection requires:
- Positive or indeterminate enzyme-linked immunosorbent assay (ELISA), AND
- Positive immunoblot blot by Centers for Disease Control and Prevention (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.

Blue Advantage will treat **polymerase chain reaction (PCR)-based direct detection of B. burgdorferi (by direct or amplified probe) in CSF samples** as a **covered benefit** and may replace serologic documentation of infection in members **with a short duration of neurologic symptoms (<14 days) during the window between exposure and production of detectable antibodies**.

Blue Advantage will treat a **single2- to 4-week course of IV antibiotics** as a **covered benefit** in members 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.

Blue Advantage will treat a **single 2- to 4-week course of IV antibiotic therapy** as a **covered benefit** in the small subset of members 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.

Blue Advantage will treat **intravenous antibiotic therapy** as a **non-covered benefit** in the following situations:

- Members with symptoms consistent with chronic fatigue syndrome or fibromyalgia, in the absence of objective clinical or laboratory evidence for Lyme disease;
- Members with seronegative LD in the absence of 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 antibiotic therapy);
- Members with vague systemic symptoms without supporting serologic or CSF studies;
- Members with a positive ELISA test, unconfirmed by an immunoblot or Western blot test (see definition above);
- Members with an isolated positive serologic test in the setting of multiple negative serologic studies;
- Members with chronic (> 6 months) subjective symptoms ("post-Lyme syndrome") after receiving recommended treatment regimens for documented LD.

Blue Advantage will treat **repeat or prolonged courses (greater than 4 weeks) of intravenous antibiotic therapy** as a **non-covered benefit.**

Blue Advantage will treat **repeat PCR-based direct detection of B. burgdorferi (by direct or amplified probe)** as a **non-covered benefit** and **investigational** in the following situations:

- As a justification for continuation of IV antibiotics beyond 1 month in patients with persistent symptoms
- As a technique to follow therapeutic response

Blue Advantage will treat **PCR-based direct detection of B. burgdorferi in urine samples** as a **non-covered benefit** and **investigational** in all clinical situations.

Blue Advantage will treat **genotyping or phenotyping of B. burgdorferi** as a **non-covered benefit** and as **investigational**.

Blue Advantage will treat **determination of levels of the B lymphocyte chemoattractant CXCL 13 for diagnosis or monitoring treatment** as a **non-covered benefit** and as **investigational**.

Blue Advantage will treat **other diagnostic testing including but not limited to "stand alone" C6 peptide ELISA** as a **non-covered benefit** and **investigational**.

Effective for dates of service February 26, 2018 through March 1, 2018, refer to LCD L33433.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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 U.S.) or Ixodes pacificus (Pacific coast, most common in Northern California) tick. The disease is characterized by stages, beginning with localized infection of the skin (erythema migrans), followed by dissemination to many sites. Diagnostic testing for Lyme disease is challenging and can lead to overdiagnosis and overtreatment.

Lyme Disease

Manifestations of early disseminated disease may include lymphocytic meningitis, facial palsy, painful radiculoneuritis, atrioventricular (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, intravenous (IV) antibiotics are indicated in some patients with neurologic involvement or atrioventricular block. The following paragraphs describe the various manifestations of Lyme disease, 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 cerebrospinal fluid (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's 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'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. Also, the symptoms are nonspecific and overlap with fibromyalgia and chronic fatigue syndrome. Thus 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 two 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. CSF abnormalities are usually seen only in those patients with a coexistent encephalopathy.

Lyme Carditis
Lyme carditis may appear during the early dissemination stage of the disease; symptoms include atrioventricular 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. Intravenous regimens are used in patients with a high-degree atrioventricular block or a PR interval on the electrocardiogram more 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 involvement, requiring IV antibiotic 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 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 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.

Diagnostic Testing
Overview
The optimum method of testing for Lyme disease 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 Lyme disease is generally based on the clinical picture and demonstration of specific antibodies (see next), polymerase chain reaction (PCR) based technology can detect the spirochete in the central nervous system 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 cerebral spinal fluid (CSF) detection in patients with suspected neuroborreliosis. Polymerase chain reaction (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 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 from 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 to establish the diagnosis of LD. 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 two-tiered method for the serologic diagnosis of LD: 1) an enzyme-linked immunosorbent assay (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; only IgG only if symptoms have been present >30 days). A negative ELISA or IFA may be followed by a later (e.g., in 4 to 6 weeks) convalescent serum test when symptoms have been present ≤30 days.

ELISA for B. Burgdorferi Antibodies
This ELISA test is a screening serologic test for Lyme disease. 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–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 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 Lyme disease 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 Centers for Disease Control and Prevention 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 Centers for Disease Control and Prevention 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. U.S. criteria for interpreting immunoblot results differ from those in Europe due to differences in prevalent Borrelia species causing disease.

Polymerase Chain Reaction (PCR)
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 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 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 two 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 three 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 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 central nervous system. 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 two 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 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 two- to four-week course of ceftriaxone or cefotaxime, or penicillin. 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. 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.

KEY POINTS:

The most recent literature review was performed through August 14, 2020.

Summary of Evidence

Suspected Lyme Disease

For individuals who are suspected of having Lyme disease who receive genotyping or phenotyping of B. burgdorferi subspecies or who receive CXCL13 gene testing or C6 peptide assay testing, the evidence is limited. Relevant outcomes are change in disease status and morbid events. Polymerase chain reaction-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 Lyme disease who receive prolonged or repeated courses of antibiotic therapy, the evidence includes randomized controlled trials (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, though in some persistent cases, a 2- to 4-week course of intravenous (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. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

It is well established that optimum method of testing depends on the stage of the disease. Guidelines from the Centers for Disease Control and Prevention 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 laboratory testing is indicated, 2-tiered serologic testing is recommended. Polymerase chain reaction (PCR), may be clinically useful as a second approach in patients with a short duration of neurologic symptoms (<14 days).

Practice Guidelines and Position Statements

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention has recommended a 2-tier process when testing blood for evidence of antibodies against the Lyme disease bacteria. Both steps can be done using the same blood sample. The first step uses a testing procedure called enzyme immunoassay or rarely, an indirect immunofluorescence assay. If this first step is negative, no further testing of the specimen is recommended. If the first step is positive or indeterminate (sometimes called "equivocal") the second step should be performed. The second step uses an immunoblot test, commonly, a Western blot test. Results are considered positive only if the enzyme immunoassay or immunofluorescence assay and the immunoblot are both positive. The Centers for Disease Control and Prevention do not recommend skipping the first test and just doing the Western blot. Doing so will increase the frequency of false-positive results and may lead to misdiagnosis and

improper treatment. New tests may be developed as alternatives to one or both steps of the 2-tier process. Before the Centers for Disease Control and Prevention recommend new tests, test performance must be demonstrated to be equal to or better than the results of the existing procedure, and they must be U.S. Food and Drug Administration approved.

Regarding treatment, the Centers for Disease Control and Prevention noted that "People with certain neurological or cardiac forms of illness may require intravenous treatment with antibiotics such as ceftriaxone or penicillin."

Infectious Diseases Society of America et al
As of August 2020, updated guidelines from the Infectious Diseases Society of America and 12 other organizations are in development.
American College of Rheumatology et al

In 1993, the American College of Rheumatology and the Infectious Diseases Society of America (IDSA) published a position paper on intravenous (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….” Other studies have also supported the use of oral, not IV, antibiotics in patients with Lyme disease without neurologic involvement.

The final publication of new guidelines for the Prevention, Diagnosis, and Treatment of Lyme Disease is anticipated in the early summer 2020.

National Institute for Health and Care Excellence
Guidance on Lyme disease from the National Institute for Health and Care Excellence (NICE)was published in 2018. NICE recommended that if “there is clinical suspicion of Lyme disease in people without erythema migrans,” “an enzyme-limked immunosorbent assay (ELISA) test for Lyme disease” should be offered. If the ELISA test is “positive pr equivocal,” an “immunoblot test” for Lyme disease should be performe. The NICE recommended oral antibiotics for the treatment of erythem migrans and/or nonfocal symptoms, and a 21-day course og IV antibiotics for Lyme disease affecting the central nervous or for Lyme carditis when the patients are hemodynamically unstable.

International Lyme and Associated Diseases Society
The International Lyme and Associated Diseases Society published guidelines in 2014 to address three clinical issues: the usefulness of antibiotic prophylaxis of tick bites, the effectiveness of erythema migrans treatment, and antibiotic retreatment in patients with persistent symptoms. The Society noted that the evidence on treatment of tick bites, erythema migrans rashes, and persistent manifestations is limited. Regarding the treatment of patients with persistent symptoms, the Society panel concluded that the evidence for retreatment is adequate to support retreatment, but is not strong enough to mandate treatment. The panel determined that there was no compelling evidence supporting withholding antibiotics from symptomatic patients, especially since there is a lack of alternative treatment options. Due to the number of clinical

variables and the heterogeneity of the patient population, clinical judgment and patients' values and goals should be considered when planning a treatment strategy.

U.S. Preventive Services Task Force Recommendations
Not applicable.

KEY WORDS:

Intravenous Antibiotic Therapy for Lyme Disease, Lyme Disease, Intravenous Antibiotic Therapy, B lymphocyte chemoattractant, C6 peptide ELISA, Chemoattractant CXCL13, CXCL 13, genotyping of B. burgdorferi, Lyme Disease, PCR based direct detection of B. burgdorferi in urine samples, phenotyping of B. burgdorferi, B. burgdorferi

APPROVED BY GOVERNING BODIES:

The FDA has cleared multiple enzyme immunoassay, 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 Lyme disease. 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.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

86617	Borrelia burgdorferi (Lyme disease) confirmatory test (e.g., Western blot or immunoblot)
87475	Infectious agent detection by nucleic acid; Borrelia burgdorferi, **direct** probe technique
87476	Infectious agent detection by nucleic acid; Borrelia burgdorferi, **amplified** probe technique
0041U	Borrelia burgdorferi, antibody detection of 5 recombinant protein groups, by immunoblot, IgM
0042U	Borrelia burgdorferi, antibody detection of 12 recombinant protein groups, by immunoblot, IgG

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POLICY HISTORY:

Adopted for Blue Advantage, June 2009
Available for comment June 26-August 9, 2009
Medical Policy Group, January 2011
Available for comment January 11, 2011 through February 21, 2011
Medical Policy Group, March 2012
Available for comment March 28 through May 15, 2012
Medical Policy Group, November 2012
Medical Policy Group, January 2014
Medical Policy Group, January 2015
Medical Policy Group, October 2015
Medical Policy Group, November 2016
Medical Policy Group, May 2017
Medical Policy Group, July 2017
Medical Policy Group, November 2017
Medical Policy Group, February 2018
Medical Policy Group, March 2018: Reinstated policy effective March 2, 2018.
Medical Policy Group, February 2021

providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.