## Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

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<td>September 30, 2015</td>
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### Policy Statement

**Lyme Disease**

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

**Neuroborreliosis**

A 2- to 4-week course of intravenous (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:
- Cranial neuropathy, other than uncomplicated cranial nerve palsy, with documented CSF abnormalities
- Encephalitis or encephalomyelitis with documented CSF abnormalities
- Lymphocytic meningitis with documented cerebrospinal fluid (CSF) abnormalities
- Polyneuropathy
- Radiculopathy

Lyme disease may be documented by 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 all of the following:
- Positive immunoblot blot by Centers for Disease Control and Prevention criteria
- Positive or indeterminate enzyme-linked immunosorbent assay (ELISA)

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

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 (less than 14 days) during the window between exposure and production of detectable antibodies.

**Lyme Carditis**

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 high degree atrioventricular block or a PR interval more than 0.3 seconds. 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 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.
Antibiotic Therapy
Intravenous antibiotic therapy is considered **not medically necessary** in the following situations:

- Patients with symptoms consistent with chronic fatigue syndrome or fibromyalgia, in the absence of objective clinical or laboratory evidence of Lyme disease
- Patients with seronegative Lyme disease in the absence of CSF antibodies
- Initial therapy in patients with Lyme arthritis without coexisting neurologic symptoms
- Cranial nerve palsy (e.g., Bell 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 IV antibiotic therapy)
- Patients with vague systemic symptoms without supporting serologic or CSF studies
- Patients with a positive enzyme-linked immunosorbent assay test (ELISA), unconfirmed by an immunoblot or Western blot test (see definition above)
- Patients with an isolated positive serologic test in the setting of multiple negative serologic studies
- Patients with chronic (greater than or equal to 6 months) subjective symptoms (“post-Lyme syndrome”) after receiving recommended treatment regimens for documented Lyme disease

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

Diagnostic Testing
Repeat PCR-based direct detection of *B. burgdorferi* is considered **investigational** in both the following situations:

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

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

Genotyping or phenotyping of *B. burgdorferi* is considered **investigational**.

Other diagnostic testing is considered **investigational** including but not limited to either of the following:

- Stand-alone” C6 peptide enzyme-linked immunosorbent assay (ELISA)
- Determination of levels of the B-lymphocyte chemoattractant CXC L13 for diagnosis or monitoring treatment

Policy Guidelines
- N/A

Description
Lyme disease 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.

Related Policies
- N/A
Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

The Food and Drug Administration 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.

Rationale

Background

Lyme Disease

Lyme disease 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, atriowentricular (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 Lyme disease can be adequately treated with oral antibiotics, intravenous (IV) antibiotics are indicated in some patients with neurologic involvement or AV block. The following paragraphs describe the various manifestations of Lyme disease, therapies, and the various laboratory tests used to support the diagnosis 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 a strong evidence against Lyme meningitis. The usual treatment consists of two 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 Lyme disease, occasionally before the development of antibodies, such that a Lyme disease 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 two 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 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 an electrocardiogram more than 0.3 seconds. 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 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 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 Lyme disease, 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 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 below), 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, the 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 with 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) 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 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% to 10%. Thus, as with any laboratory test, interpretation of serologic tests requires a 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 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 recommend a 2-tiered method for the serologic diagnosis of Lyme disease: (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 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 two of the three most common IgM antibody bands to spirochetal antigens are present, or five of the ten most frequent IgG antibody bands are present. Because the 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
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 the 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 various 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 two 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 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 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 various 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 is a potential marker for successful treatment.

Treatment of Lyme Disease
As noted, treatment with IV antibiotics may be indicated only in patients with symptoms and laboratory findings consistent with the central nervous system 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 Lyme disease. 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.

Literature Review
Suspected Lyme Disease
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome.
That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Analysis of *Borrelia Burgdorferi* Genotype**

**Clinical Context and Therapy Purpose**

The purpose of genotyping or phenotyping of *Borrelia burgdorferi* subspecies testing in patients suspected of having Lyme disease is to inform an accurate diagnosis and, if positive, to initiate a treatment regimen.

The question addressed in this evidence review is: Does the use of genotyping or phenotyping of *Borrelia burgdorferi* subspecies improve the net health outcome of those suspected of having Lyme disease?

The following PICO(s) were used to select literature to inform this review.

**Patients**

The relevant population of interest are individuals with suspected Lyme disease.

**Interventions**

The tests being considered are genotyping or phenotyping of *Borrelia burgdorferi* subspecies.

**Comparators**

The following practice is currently being used to diagnose Lyme disease: established, tiered diagnostic approach using enzyme-linked immunosorbent assay and confirmatory Western blot.

**Outcomes**

The general outcome of interest is the diagnostic accuracy of the test to identify those with or without Lyme disease.

Follow-up over several weeks to months would be needed to confirm test findings and conduct further testing. Long-term follow-up may be necessary to monitor for residual symptoms (e.g., joint inflammation, encephalopathy) after the active infection has been eliminated.

**Study Selection Criteria**

For the evaluation of clinical validity of genotyping or phenotyping of *Borrelia burgdorferi* subspecies, methodologically credible studies were selected using the following principles:

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and
unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Polymerase chain reaction-based technology has been used as a step in the genotypic analysis of *Borrelia burgdorferi*. *B. burgdorferi* was originally characterized as a single species (*B. burgdorferisensulato*), but genotypic analysis has revealed that this group represents four distinct species and genomic groups. Of these, the following have been isolated from patients with Lyme disease: *B. burgdorferisensustricto*, *B. garinii*, *B. afzelii*, and *B. bavariensis*. The prevalence of these genospecies may vary among populations and may be associated with different clinical manifestations.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

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. burgdorferisensustricto* and *B. mayonii* are the only human pathogenic species, but in Europe, all three species cause infection. A study by Wilske et al (2007) reported that *B. spielmanii* was found in a small number of European patients; accordingly, criteria for interpreting immunoblot results differ in Europe than in the U. S.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Because the clinical validity of genotyping or phenotyping of *Borrelia burgdorferi* subspecies has not been established, a chain of evidence cannot be established.

**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. The evidence is insufficient to demonstrate that the intervention improves net health outcomes.

**CXCL13 Chemokine Concentration Testing and Stand-Alone C6 Peptide Testing**

**Clinical Context and Therapy Purpose**
The purpose of CXCL13 levels or C6 peptide assay testing in patients suspected of having Lyme disease is to inform an accurate diagnosis and, if positive, to initiate a treatment regimen.

The question addressed in this evidence review is: Does the use of testing for CXCL13 chemokine concentration or C6 peptide assay testing improve the net health outcome of those suspected of having Lyme disease?

The following PICOs were used to select literature to inform this review.
Patients
The relevant population of interest are individuals with suspected Lyme disease.

Interventions
The test being considered is testing for CXCL13 chemokine concentration or C6 peptide assay testing.

Comparators
The following practice is currently being used to diagnose Lyme disease: established, tiered diagnostic approach using enzyme-linked immunosorbent assay and confirmatory Western blot.

Outcomes
The general outcome of interest is the diagnostic accuracy of the test to identify those with or without Lyme disease.

Follow-up over several weeks to months would be needed to confirm test findings and conduct further testing. Long-term follow-up may be necessary to monitor for residual symptoms (e.g., joint inflammation, encephalopathy) after the active infection has been eliminated.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

CXCL13 chemokine 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 enzyme immunoassay (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 (enzyme-linked immunosorbent assay) followed by C6 EIA, and found the specificity and positive predictive values were comparable with the 2-tiered enzyme-linked immunosorbent assay-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 Lyme disease. 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 systematic review by Sanchez et al (2016), which assessed the diagnosis and treatment of Lyme disease, also concluded that “stand-alone” C6 testing is not recommended over the 2-tiered approach due to slightly lower specificity.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of CXCL13 chemokine concentration levels and C6 peptide assay testing were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Because the clinical validity of CXCL13 concentration testing and C6 peptide assay testing have not been established, a chain of evidence cannot be established.

**Section Summary: CXCL13 Chemokine and C6 Peptide**
Data are limited on the determination of CXCL13 levels in patients suspected of having Lyme disease. 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**
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Clinical Context and Test Purpose**
The purpose of prolonged or repeated courses of antibiotic therapy in patients with confirmed Lyme disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of prolonged or repeated courses of antibiotic therapy improve the net health outcome of those with confirmed Lyme disease?

The following PICOs were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with confirmed Lyme disease.

**Interventions**
The therapy being considered is prolonged or repeated courses of antibiotic therapy.

**Comparators**
The following therapies are currently being used to treat confirmed Lyme disease: a standard course of oral antibiotic therapy and a 2- to 4-week course of intravenous antibiotic therapy. The diagnosis and treatment of Lyme disease are by primary care clinicians and infectious disease specialists generally in the outpatient setting.

**Outcomes**
The general outcomes of interest are disease remission and symptom reduction. Follow-up over the long-term may be necessary to monitor for residual symptoms (e.g., joint inflammation, encephalopathy).
Role of Intravenous or Prolonged Oral Antibiotic Therapy

The evidence does not support the use of recommended antibiotic therapy to treat patients with persistent *B. burgdorferi* infection and well-documented Lyme disease.11. See Tables 1 and 2, which summarizes the characteristics and results of blinded, RCTs of extended antibiotic therapy vs placebo in such patients. The evidence has provided inconsistent results.

While morphologic variants of *B. burgdorferi* are thought to be related to persistent Lyme disease symptoms, a systematic review by Lantos et al (2014) found no evidence to support this.12. Reviewers found no pathogenic relation between morphologic variants of *B. burgdorferi* and persistent symptoms of Lyme disease. Additionally, no literature was identified that would support a role for treatment of *B. burgdorferi* morphologic variants.

Table 1. Summary of Randomized Controlled Trial Characteristics: Prolonged Antibiotic Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Interventions</th>
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<tr>
<td>Berende et al (2016)</td>
<td>280 patients with persistent Lyme disease symptoms given IV ceftriaxone for 2 wk</td>
<td>Doxycycline or clarithromycin/hydroxychloroquine for 12 wk</td>
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<tr>
<td>Fallon et al (2008)</td>
<td>37 patients with documented objective memory impairment</td>
<td>IV ceftriaxone daily for 70 d</td>
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<tr>
<td>Cameron (2008)</td>
<td>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)</td>
<td>Oral amoxicillin 3 g daily for 3 mo (34 assigned, 17 evaluable)</td>
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<tr>
<td>Oksi et al (2007)</td>
<td>152 consecutive patients treated with standard antibiotic regimen for 21 d</td>
<td>Amoxicillin twice daily for 100 d starting immediately after standard regimen</td>
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<tr>
<td>Kaplan et al (2003)</td>
<td>129 patients (same trial as Klempner et al [2001])</td>
<td>Placebo twice daily for 100 d starting immediately after standard regimen</td>
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<tr>
<td>Krupp et al (2003)</td>
<td>Patients with persistent severe fatigue ≥6 mo</td>
<td>IV ceftriaxone daily for 28 d</td>
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<tr>
<td>Klempner et al (2001)</td>
<td>78 positive for IgG to <em>B. burgdorferi</em>; persistent symptoms interfered with patient functioning</td>
<td>IV ceftriaxone daily for 30 d and oral doxycycline for 60 d</td>
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<td>51 patients negative for IgG to <em>B. burgdorferi</em>; else, as above</td>
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IgG: immunoglobulin G; IV: intravenous.

Table 2. Summary of Randomized Controlled Trial Results: Prolonged Antibiotic Therapy

<table>
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<tr>
<th>Study</th>
<th>Results</th>
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<tr>
<td>Berende et al (2016)</td>
<td>• SF-36 PCS did not differ across 3 study groups</td>
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<tr>
<td></td>
<td>• Adverse event rates similar across 3 study groups</td>
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<tr>
<td></td>
<td>• 4 serious ceftriaxone-related adverse events</td>
</tr>
<tr>
<td>Fallon et al (2008)</td>
<td>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 differ marginally at week 12 (p=0.05). Exploratory subgroup analyses suggested significantly</td>
</tr>
</tbody>
</table>
better improvement in ceftriaxone-treated patients with more severe baseline pain and physical functioning.

- 44% of enrolled patients inevaluable at 6 mo; 17 had poorer baseline QOL and were lost due to treatment failure
- SF-36 improvements for antibiotic vs placebo arm were significant (46% vs 18%, p=0.007), but unclear whether analysis included all or only evaluable patients
- 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)

Oksi et al (2007)¹⁶

Both treatment and control arms showed similar and not significantly different decreases in patient- and investigator-reported VAS outcomes (VAS range, 0-100; 0=no symptoms) at 12 mo. B. burgdorferi-specific antibodies declined similarly in both groups over 12 mo.

Kaplan et al (2003)¹⁷

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.


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.

Klemperer et al (2001)¹⁸

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.

BDI: Beck Depression Inventory; 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.

Section Summary: Role of Intravenous or Prolonged Oral Antibiotic Therapy

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

Summary of Evidence

For individuals who are suspected of having Lyme disease who receive genotyping or phenotyping of B. burgdorferi subspecies or who receive CXCL13 chemokine concentration testing or C6 peptide assay testing, the evidence is limited. The relevant outcomes are a 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 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 RCTs. The 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 antibiotics may be appropriate. Evidence from RCTs has not shown a benefit in prolonged (>4 weeks) or repeat courses of oral or intravenous antibiotics. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Supplemental Information

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 does 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 recommends new tests, test performance must be demonstrated to be equal to or better than the results of the existing procedure, and they must be approved by the U.S. Food and Drug Administration.

Infectious Diseases Society of America
As of August 2019, updated guidelines from the Infectious Diseases Society of America and 12 other organizations are in development.

American College of Rheumatology et al
The American College of Rheumatology and the Infectious Diseases Society of America (1993) 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 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 late 2019.

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

International Lyme and Associated Diseases Society
The International Lyme and Associated Diseases Society (2014) published guidelines to address 3 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 concluded that the evidence for retreatment is adequate to support retreatment, but is not strong enough to mandate treatment. The Society 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.

**Medicare National Coverage**
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.

**Ongoing and Unpublished Clinical Trials**
Some currently ongoing or unpublished trials that might influence this review are listed in Table 3.

<table>
<thead>
<tr>
<th>Table 3. Summary of Key Trials</th>
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</thead>
<tbody>
<tr>
<td><strong>NCT No.</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Ongoing</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Industry sponsored or partially sponsored.

**References**


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Documented objective neurologic findings
- Documentation of CSF abnormalities
- Serologic documentation of infection
- Symptom presentation with recent tick bite or exposure with erythema migrans rash
- Diagnostic testing (i.e., ELISA, Western blot, PCR) if not able to diagnosis clinically
- Reason for request
- Treatment plan

**Post Service**
- Diagnostic testing
- Treatment

### Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0041U</td>
<td>Borrelia burgdorferi, antibody detection of 5 recombinant protein groups, by immunoblot, IgM (Code effective 4/1/2018)</td>
</tr>
<tr>
<td></td>
<td>0042U</td>
<td>Borrelia burgdorferi, antibody detection of 12 recombinant protein groups, by immunoblot, IgG (Code effective 4/1/2018)</td>
</tr>
<tr>
<td></td>
<td>0043U</td>
<td>Tick-borne relapsing fever Borrelia group, antibody detection to 4 recombinant protein groups, by immunoblot, IgM (Code effective 4/1/2018)</td>
</tr>
<tr>
<td></td>
<td>0044U</td>
<td>Tick-borne relapsing fever Borrelia group, antibody detection to 4 recombinant protein groups, by immunoblot, IgG (Code effective 4/1/2018)</td>
</tr>
<tr>
<td></td>
<td>86617</td>
<td>Antibody; Borrelia burgdorferi (Lyme disease) confirmatory test (e.g., Western Blot or immunoblot)</td>
</tr>
<tr>
<td></td>
<td>87475</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Borrelia burgdorferi, direct probe technique</td>
</tr>
<tr>
<td></td>
<td>87476</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Borrelia burgdorferi, amplified probe technique</td>
</tr>
<tr>
<td></td>
<td>87477</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Borrelia burgdorferi, quantification (Deleted code effective 1/1/2018)</td>
</tr>
<tr>
<td></td>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>3E03329</td>
<td>Introduction of Other Anti-Infective into Peripheral Vein, Percutaneous Approach</td>
</tr>
</tbody>
</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.
Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.