

Medical Policy



Title: Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are suspected of having Lyme disease	Interventions of interest are: • Genotyping or phenotyping of <i>Borrelia burgdorferi</i> subspecies	Comparators of interest are: • Established, tiered diagnostic approach	Relevant outcomes include: • Change in disease status • Morbid events
Individuals: • Who are suspected of having Lyme disease	Interventions of interest are: • CXCL13 chemokine concentration testing • Stand-alone C6 peptide assay testing	Comparators of interest are: • Established, tiered diagnostic approach	Relevant outcomes include: • Test accuracy • Change in disease status • Morbid events
Individuals: • With confirmed Lyme disease	Interventions of interest are: • Prolonged or repeated courses of antibiotic therapy	Comparators of interest are: • Standard course of oral antibiotic therapy • Two- to 4-week course of intravenous antibiotic therapy	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Health status measures

DESCRIPTION

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, 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 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 strong evidence against Lyme meningitis. Usual treatment consists of 2 weeks of either oral (ambulatory setting) or IV (hospitalized patients) antibiotics.

Cranial neuritis, most frequently Bell palsy, may present early in the course of disseminated 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 2 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.^{1,2} However, while PCR-based tests can identify organisms in skin biopsy specimens of patients with dermatologic manifestations (ie, erythema migrans), this diagnosis is typically made clinically, and antibiotic therapy is started empirically.

Similarly, diagnosis of Lyme arthritis is based on clinical and serologic studies without the need for synovial tissue or fluid. Finally, intrathecal antibody production is considered a more sensitive test than PCR-based CSF detection in patients with suspected neuroborreliosis. PCR may be clinically useful as a second approach in patients with a short duration of neurologic symptoms (<14 days) during the window between exposure and the emergence of detectable levels of antibodies in the CSF.³ 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, 1 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 (eg, 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 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 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 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 2 weeks of infection, but after that the detection rate is low. PCR is not recommended for urine or blood specimens. However,

PCR-based direct detection of *B. burgdorferi* in the blood may be useful for documenting Lyme carditis when results of serologic studies are equivocal.

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

T-Cell Proliferative Assay

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

Evaluation of CSF

Aside from the standard evaluation of CSF for pleocytosis, protein levels, and glucose levels, various tests are available to determine whether anti-*B. burgdorferi* antibodies are being selectively produced within the 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 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 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.

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.

POLICY

IV Antibiotic Therapy

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

Neuroborreliosis

- I. 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).
 1. Objective neurologic findings include:
 - a. Lymphocytic meningitis with documented cerebrospinal fluid (CSF) abnormalities
 - b. Cranial neuropathy, other than uncomplicated cranial nerve palsy, with documented CSF abnormalities
 - c. Encephalitis or encephalomyelitis with documented CSF abnormalities
 - d. Radiculopathy
 - e. Polyneuropathy
 2. 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 infection, as indicated above.
 3. Serologic documentation of infection requires:
 - a. Positive or indeterminate enzyme-linked immunosorbent assay (ELISA), AND
 - b. Positive immunoblot blot by Centers for Disease Control and Prevention criteria
 4. Documented CSF abnormalities include **ALL** of the following:
 - a. Pleocytosis
 - b. Evidence of intrathecal production of *Borrelia burgdorferi* antibodies in CSF; and
 - c. Increased protein levels
 5. 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.

Lyme Carditis

- II. 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 second. 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

- III. 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

- IV. 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 of 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 (eg, Bell 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
- V. Repeat or prolonged courses (eg, >4 weeks) of IV antibiotic therapy are considered **not medically necessary**.

Diagnostic Testing

- I. Repeat PCR-based direct detection of *B. burgdorferi* is considered **experimental / investigational** in the following situations:
 1. As a justification for the continuation of IV antibiotics beyond 1 month in patients with persistent symptoms
 2. As a technique to follow therapeutic response
- II. PCR-based direct detection of *B. burgdorferi* in urine samples is considered **experimental / investigational** in all clinical situations.
- III. Genotyping or phenotyping of *B. burgdorferi* is considered **experimental / investigational**.
- IV. Other diagnostic testing is considered **experimental / investigational** including but not limited to “stand-alone” C6 peptide ELISA or determination of levels of the B-lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through August 6, 2018.

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.

Clinical Context and Therapy Purpose

The purpose of genotyping or phenotyping of *Borrelia burgdorferi* subspecies or 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 genotyping or phenotyping of *Borrelia burgdorferi* subspecies or testing for CXCL13 chemokine concentration or C6 peptide assay testing improve the net health outcome of those suspected of having Lyme disease?

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

Patients

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

Interventions

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

Outcomes

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

Timing

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 (eg, joint inflammation, encephalopathy) after the active infection has been eliminated.

Setting

The diagnosis and treatment of Lyme disease is by primary care clinicians and infectious disease specialists generally in the outpatient setting. The testing is performed by commercial laboratories.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires 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.

Analysis of *Borrelia Burgdorferi* Genotype

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. burgdorferi sensu lato*), but genotypic analysis has revealed that this group represents 4 distinct species and genomic groups. Of these, the following have been isolated from patients with Lyme disease: *B. burgdorferi sensu stricto*, *B. garinii*, *B. afzelii*, and *B. bavariensis*. The prevalence of these genospecies may vary among populations and may be associated with different clinical manifestations.⁴

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 United States, *B. burgdorferi sensu stricto* and *B. mayonii*⁵ are the only human pathogenic species, but in Europe, all 3 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 United States.⁶

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.

CXCL13 Chemokine Concentration Testing and Stand-Alone C6 Peptide Testing

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.⁷ 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.^{2,8} 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).⁸ Lipsett et al (2016) evaluated C6 EIA in 944 children of whom 114 (12%) had Lyme disease.⁹ 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.¹⁰

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 CXCL 13 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 a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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 PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is 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.

Outcomes

The general outcomes of interest are disease remission and symptom reduction.

Timing

Follow-up over the long term may be necessary to monitor for residual symptoms (eg, joint inflammation, encephalopathy).

Setting

The diagnosis and treatment of Lyme disease is by primary care clinicians and infectious disease specialists generally in the outpatient setting. The testing is performed by commercial laboratories.

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

Study	Participants	Interventions	
		Active	Comparator
Berende et al (2016) ¹³	280 patients with persistent Lyme disease symptoms given IV ceftriaxone for 2 wk	Doxycycline or clarithromycin/hydroxyl-chloroquine for 12 wk	Placebo
Fallon et al (2008) ¹⁴	37 patients with documented objective memory impairment	IV ceftriaxone daily for 70 d	IV placebo daily for 70 d
Cameron (2008) ¹⁵	86 patients with symptoms of arthralgia, cardiac, or neurologic involvement with or without fatigue after previous successful antibiotic treatment of Lyme disease; study conducted in a primary care internal medicine practice (52 assigned, 31 evaluable)	Oral amoxicillin 3 g daily for 3 mo (34 assigned, 17 evaluable)	Oral placebo daily for 3 mo
Oksi et al (2007) ¹⁶	152 consecutive patients treated with standard antibiotic regimen for 21 d	Amoxicillin twice daily for 100 d starting immediately after standard regimen	Placebo twice daily for 100 d starting immediately after standard regimen
Kaplan et al (2003) ¹⁷	129 patients (same trial as Klempner et al [2001]) ¹⁸		
Krupp et al (2003) ¹⁹	Patients with persistent severe fatigue ≥6 mo	IV ceftriaxone daily for 28 d	IV placebo
Klempner et al (2001) ¹⁸	<ul style="list-style-type: none"> • 78 positive for IgG to <i>B. burgdorferi</i>; persistent symptoms interfered with patient functioning • 51 patients negative for IgG to <i>B. burgdorferi</i>; else, as above 	<ul style="list-style-type: none"> • IV ceftriaxone daily for 30 d • oral doxycycline for 60 d 	IV and oral placebo

IgG: immunoglobulin G; IV: intravenous.

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

Study	Results
Berende et al (2016) ¹³	<ul style="list-style-type: none"> • SF-36 PCS did not differ across 3 study groups • Adverse event rates similar across 3 study groups • 4 serious ceftriaxone-related adverse events
Fallon et al (2008) ¹⁴	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 better improvement in ceftriaxone-treated patients with more severe baseline pain and physical functioning.
Cameron (2008) ¹⁵	<ul style="list-style-type: none"> • 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)

Study	Results
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. <i>B. burgdorferi</i> -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
Krupp et al (2003) ¹⁹	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.
Klempner 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. 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 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. 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.

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.²⁰ 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 et al

As of September 2018, updated guidelines from the Infectious Diseases Society of America and 12 other organizations are in development.²¹

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 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...."²² Other studies have also supported the use of oral, not IV, antibiotics in patients with Lyme disease without neurologic involvement.²³⁻²⁵

National Institute for Health and Care Excellence

Guidance on Lyme disease from the National Institute for Health and Care Excellence (NICE) was published in 2018.²⁶ 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 ELISA test is "positive or equivocal," an "immunoblot test" for Lyme disease should be performed. NICE 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.²⁷ 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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03581279 ^a	Detection of Borrelia Bacteria in Early Stage Lyme Borreliosis Using the T2Lyme Panel	300	Oct 2019
Unpublished			

NCT: national clinical trial.

^a Industry sponsored or partially sponsored.

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
- 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)
- 0041U *Borrelia burgdorferi*, antibody detection of 5 recombinant protein groups, by immunoblot, IgM [Lyme ImmunoBlot IgM Manufacturer- IGeneX Inc, ID-FISH Technology Inc.]
- 0042U *Borrelia burgdorferi*, antibody detection of 12 recombinant protein groups, by immunoblot, IgG [Lyme ImmunoBlot IgG Manufacturer- IGeneX Inc, ID-FISH Technology Inc.]
- 0043U Tick-borne relapsing fever *Borrelia* group, antibody detection to 4 recombinant protein groups, by immunoblot, IgM [Tick-Borne Relapsing Fever (TBRF) *Borrelia* ImmunoBlots IgM Test Manufacturer- IGeneX Inc, ID-FISH Technology Inc.]
- 0044U Tick-borne relapsing fever *Borrelia* group, antibody detection to 4 recombinant protein groups, by immunoblot, IgG [Tick-Borne Relapsing Fever (TBRF) *Borrelia* ImmunoBlots IgG Test Manufacturer- IGeneX Inc, ID-FISH Technology Inc.]

ICD-10 Diagnoses (Effective October 1, 2015)

- 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: <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ ICD-10 Diagnoses codes added

02-01-2017	<p>Description section updated</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ Added the sub-heading "IV Antibiotic Therapy" ahead of the policy statements I through VI. ▪ Added the sub-heading "Diagnostic Testing" and renumbered the remaining policy statements to I through IV. ▪ The following updates were made with no change to policy intent: <ul style="list-style-type: none"> ▪ In Item I replaced "IV" with "intravenous" ▪ In Item I 2 replaced "CNS" with "central nervous system" ▪ In Item I 3 replaced "CDC" with "Centers for Disease Control and Prevention" ▪ In Item II replaced "greater" with "more" ▪ In Item V replaced "greater than" with ">" ▪ In Item IX added "stand-alone" to read "...stand-alone" C6 peptide ELISA"... <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Coding notation removed <p>References updated</p>
04-11-2018	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT Codes: 0041U, 0042U, 0043U, 0044U (Effective 04-01-2018)
11-20-2018	<p>Description section updated</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ Added the following headers to define each section: Neuroborreliosis, Lyme Carditis, Lyme Arthritis, Antibiotic Therapy ▪ In Item I 2 replaced "by" with "on the basis of" to read "Lyme disease may be documented on the basis of serologic testing..." <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Deleted termed CPT code: 87477 ▪ Updated CPT nomenclature: 87476, 0041U, 0042U, 0043U, 0044U <p>Rationale updated</p>

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