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

**Professional**

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<td>Individuals: • Who are suspected of having Lyme disease</td>
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<td>Comparators of interest are: • Established, tiered diagnostic approach</td>
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<td>Relevant outcomes include: • Test accuracy • Change in disease status • Morbid events</td>
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<tr>
<td>Individuals: • With confirmed Lyme disease</td>
<td>Interventions of interest are: • Prolonged or repeated courses of antibiotic therapy</td>
<td>Comparators of interest are: • Standard course of oral antibiotic therapy • Two- to 4-week course of intravenous antibiotic therapy</td>
<td>Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Health status measures</td>
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DESCRIPTION

Lyme disease is a multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi* and transmitted by the bite of an infected *Ixodes scapularis* (northeastern U.S.) or *Ixodes pacificus* (Pacific coast, most common in Northern California) tick. The disease is characterized by stages, beginning with localized infection of the skin (erythema migrans), followed by dissemination to many sites. Diagnostic testing for Lyme disease is challenging and can lead to overdiagnosis and overtreatment.

Lyme disease 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 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.

Neurologic Manifestations of Lyme Disease (Neuroborreliosis)

Lymphocytic meningitis, characterized by head and neck pain, may occur during the acute disseminated stage of the disease. Analysis of the cerebrospinal fluid (CSF) is indispensable for the diagnosis of Lyme meningitis. If the patient has Lyme disease, the CSF will show a lymphocytic pleocytosis (lymphocyte count greater than normal) with increased levels of protein. Intrathecal production of antibodies directed at spirochetal antigens is typically present. A normal CSF analysis is strong evidence against Lyme meningitis. 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. In addition, the symptoms are nonspecific and overlap with fibromyalgia and chronic fatigue syndrome. Thus diagnosis of Lyme encephalopathy may be difficult and may best be made with a mental status exam or neuropsychological testing. However, treatment with IV antibiotics is generally not indicated unless CSF abnormalities are identified.

Much rarer, but of greater concern, is the development of encephalomyelitis, characterized by spastic paraparesis, ataxias, cognitive impairment, bladder dysfunction, and cranial neuropathy. CSF examination reveals 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.

**Cardiac Manifestations of Lyme Disease**

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. Intravenous regimens are typically used in patients with high degree AV block or a PR interval on the electrocardiogram more than 0.3 seconds. Patients with milder forms of carditis may be treated with oral antibiotics.

**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 1 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 Tests**

**Overview**
The optimum method of testing for Lyme disease depends on the stage of the disease. Diagnostic testing may not be necessary when a diagnosis can be made clinically in patients with a recent tick bite or exposure and the presence of the characteristic rash of erythema migrans. While diagnosis of Lyme disease is generally based on the clinical picture and demonstration of specific antibodies (see next), polymerase chain reaction (PCR)–based technology can detect the spirochete in the central nervous system (CNS) in cases of neuroborreliosis, in the synovial fluid of cases of Lyme arthritis, and rarely in skin biopsy specimens of those with atypical dermatologic manifestations. However, while PCR-based tests can identify organisms in skin biopsy specimens of patients with dermatologic manifestations (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 cerebral spinal fluid (CSF) detection in patients with suspected neuroborreliosis. PCR may be clinically useful as a second approach in patients with a short duration of neurologic symptoms (<14 days) during the window between exposure and the emergence of detectable levels of antibodies in the CSF. PCR-based detection is typically not performed in the urine due to the variable presence of endogenous polymerase inhibitors that affect test sensitivity.

**Serologic Tests**
The antibody response to infection with *B. burgdorferi* follows a typical pattern. During the first few weeks after the initial onset of infection, there is no antibody production. The specific immunoglobulin M (IgM) 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 close correlation with the patient’s signs and symptoms. For example, patients with vague symptoms of Lyme disease, chronic fatigue syndrome, or fibromyalgia may undergo multiple serologic tests over many weeks to months in an effort to establish the diagnosis of Lyme disease. Necessarily, 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 (CDC) recommend a 2-tiered method for the serologic diagnosis of Lyme disease: (1) ELISA or immunofluorescence assay (IFA), followed by (2) a confirmatory Western blot (including both IgM and IgG when signs or symptoms have been present ≤30 days; IgG only if for symptoms >30 days). A negative ELISA or IFA 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. In addition, 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 CDC criteria, the test result is considered positive if 2 of the 3 most common IgM antibody bands to spirochetal antigens are present, or 5 of the 10 most frequent IgG antibody bands are present. Because CDC criteria were developed for surveillance, they are conservative and may miss true 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. In addition, the test cannot distinguish between live spirochetes or fragments of dead ones. The PCR technique has been studied using a variety of specimens. PCR has the best detection rates for skin biopsies from patients with erythema migrans (but may not be indicated with recent history of tick bite or exposure) and for synovial tissue (and synovial fluid, to a lesser extent) from patients with Lyme
arthritis. CSF may be positive by PCR during the first 2 weeks of infection, but thereafter the detection rate is low. PCR is not recommended for urine or blood specimens. However, PCR-based direct detection of *B. burgdorferi* in the blood may be useful for documenting Lyme carditis when results of serologic studies are equivocal.

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

**T-Cell Proliferative Assay**

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

**Evaluation of CSF**

Aside from the standard evaluation of CSF for pleocytosis, protein levels, and glucose levels, various tests are available to determine whether anti-*B. burgdorferi* antibodies are being selectively produced within the CNS. Techniques include a variety of immunoassays. For example, intrathecal antibody production can be detected by the CSF/serum index of *B. burgdorferi* antibodies. CSF and serum samples diluted to match the total IgG concentration in CSF are run in parallel in an IgG ELISA. Excess *Borrelia*-specific antibody in CSF indicates a positive result. As noted, PCR can also be used to detect the spirochete in the CSF, most successfully within the first 2 weeks of infection.

**Evaluation of the Chemoattractant CXCL13**

CXCL13 is a B-lymphocyte chemoattractant and has been reported to be elevated in acute neuroborreliosis and a potential marker for successful treatment.

**Treatment of Lyme Disease**

As previously noted, treatment with IV antibiotics may be indicated only in patients with symptoms and laboratory findings consistent with CNS or peripheral neurologic involvement and in a small subset of patients with heart block or documented Lyme arthritis who have not responded to oral antibiotics. Typical IV therapy consists of a 2- to 4-week course of ceftriaxone or cefotaxime or penicillin. No data suggest that prolonged or repeated courses of IV antibiotics are effective. Lack of effect should suggest an incorrect diagnosis or slow resolution of symptoms, which is commonly seen in Lyme disease. In addition, some symptoms may persist after treatment, such as Lyme arthritis; this phenomenon may be related to various self-sustaining inflammatory mechanisms rather than persistent infection.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratory testing for Lyme disease is available under the auspices of CLIA. Laboratories that offer LDTs must
be licensed by CLIA for high-complexity testing. As of 2014, there were at least 70 approved commercial laboratories that perform serologic testing for Lyme disease.\(^4\) To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**POLICY**

**IV Antibiotic Therapy**

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

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. Polineuropathy

2. Lyme disease may be documented on the basis of serologic testing or by clinical findings of erythema migrans in early infection. Documentation of CSF abnormalities is required for suspected central nervous system 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.
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 a high degree atrioventricular block or a PR interval of 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.

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.

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 for Lyme disease
2. Patients with seronegative Lyme disease in the absence of CSF antibodies
3. Initial therapy in patients with Lyme arthritis without coexisting neurologic symptoms
4. Cranial nerve palsy (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 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 regularly with searches of the MEDLINE database. The most recent literature update was performed through August 25, 2016. The following is a summary of the key literature to date.

ANALYSIS OF *BORRELIA BURGDORFERI* GENOTYPE
Polymerase chain reaction (PCR)–based technology has been used as 1 step in the genotypic analysis of *Borrelia burgdorferi*. *B. burgdorferi* was originally characterized as a single species (*B. burgdorferi sensu lato*), but genotypic analysis has revealed that this group represents 4 distinct species and genomic groups. Of these, the following have been isolated from patients with 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. However, no data were found in the published literature regarding whether or how knowledge of the genotype or phenotype of *B. burgdorferi* could be used to improve patient management and outcomes. In the United States, *B. burgdorferi sensu stricto* and *B. mayonii* are the only human pathogenic species, but in Europe, all 3 species cause infection. In 2007, *B. spielmanii* was found in a small number of European patients; therefore, criteria for interpreting immunoblot results differ in Europe than in the United States.

Section Summary: Analysis of *Borrelia Burgdorferi* Genotype
No data were found in the published literature regarding whether or how knowledge of the genotype or phenotype of *B. burgdorferi* could be used to improve patient management and outcomes
CHEMOKINE CXCL13 AND C6 PEPTIDE
CXCL13 is a B-lymphocyte chemoattractant that has been reported to be elevated in acute neuroborreliosis,\(^8\) thus it is 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.\(^2,9\) Branda et al (2011) reported on the use of whole-cell sonicate EIA (enzyme-linked immunosorbent assay [ELISA]) followed by C6 EIA and found the specificity and positive predictive values were comparable with the 2-tiered ELISA-Western blot approach (99.5% vs 98.4%, and 70% vs 66%, respectively).\(^9\) Lipsett et al (2016) evaluated C6 EIA in 944 children of whom 114 (12%) had Lyme disease.\(^10\) They found stand-alone C6 EIA testing had lower specificity than 2-tiered testing (94.2% vs 98.8%); specificity was increased to 98.6% with a supplemental immunoblot. A 2016 systematic review of 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.\(^11\)

Section Summary: Chemokine CXCL13 and C6 peptide
Data on the determination of CXCL 13 levels in patients suspected of having Lyme disease is limited. Additional research is necessary to determine diagnostic and treatment utility. Stand-alone C6 testing is not recommended over the 2-tier approach.

ROLE OF INTRAVENOUS OR PROLONGED ORAL ANTIBIOTIC THERAPY
The evidence generally does not support persistent \textit{B. burgdorferi} infection in patients with well-documented infection who have received recommended antibiotic therapy.\(^12\) Blinded, randomized controlled trials (RCTs) of extended antibiotic therapy versus placebo in such patients have shown no consistent differences in outcomes (summarized in Table 1).

While morphologic variants of \textit{B. burgdorferi} are thought to be related to persistent Lyme disease symptoms, a 2014 systematic review by Lantos et al found no evidence to support this.\(^13\) The reviewers found no pathogenic relation between morphologic variants of \textit{B. burgdorferi} and persistent symptoms of Lyme disease. Additionally, no literature was identified that would support a role for treatment of \textit{B. burgdorferi} morphologic variants.

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 (IV) antibiotics may be appropriate. Evidence from RCTs has not shown a benefit to prolonged (>4 weeks) or repeat courses of oral or IV antibiotics.
Table 1. Summary of Randomized Controlled Trials of Prolonged Antibiotic Therapy in Patients With Well-Documented, Previously Treated Lyme Disease

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<tr>
<th>Study</th>
<th>N</th>
<th>Patient Description</th>
<th>Experimental Treatment</th>
<th>Control Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klempner et al (2001)(^{14})</td>
<td>78</td>
<td>(1) Positive for IgG to <em>B. burgdorferi</em>; persistent symptoms that interfered with patient function (2) Negative for IgG to <em>B. burgdorferi</em>; else, as above</td>
<td>IV ceftriaxone daily for 30 d, oral doxycycline for 60 d</td>
<td>IV and oral placebos</td>
<td>No significant difference in QOL outcomes for 1 or 2. Studies terminated after interim analyses indicated it was highly unlikely that a significant difference in treatment efficacy would be observed.</td>
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<td>Kaplan et al (2003)(^{15})</td>
<td>129</td>
<td>Same trial as Klempner et al (2001)(^{14})</td>
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<td></td>
<td>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</td>
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<tr>
<td>Krupp et al (2003)(^{16})</td>
<td>55</td>
<td>Patients with persistent severe fatigue ≥6 mo</td>
<td>IV ceftriaxone daily for 28 d</td>
<td>IV placebo</td>
<td>Ceftriaxone treatment arm showed no significant improvement in primary outcome of laboratory measure of persistent infection. Significant improvement in secondary outcome of 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.</td>
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<tr>
<td>Oksi et al (2007)(^{17})</td>
<td>152</td>
<td>Consecutive patients treated with standard antibiotic regimen for 21 d</td>
<td>Amoxicillin twice daily for 100 d starting immediately after standard regimen</td>
<td>Placebo twice daily for 100 d starting immediately after standard regimen</td>
<td>Both treatment and control arms showed similar and not significantly different decreases in patient and investigator VAS outcomes (VAS evaluation of symptoms, range, 0-100; 0=no symptoms) at 12 mo. <em>B. burgdorferi</em>-specific antibodies declined similarly in both groups over 12 mo.</td>
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<tr>
<td>Fallon et al (2008)</td>
<td>37</td>
<td>Patients with documented objective memory impairment</td>
<td>IV ceftriaxone daily for 70 d</td>
<td>IV placebo daily for 70 d</td>
<td>Primary outcome of cognitive function across 6 domains similarly improved in both groups at week 24 and not significantly different between groups; improvement between groups marginally significantly different at week 12 (p=0.05). Exploratory subgroup analyses suggested significantly better improvement in ceftriaxone-treated patients with more severe baseline pain and physical functioning.</td>
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| Cameron (2008)         | 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 | • 44% of enrolled patients not evaluable at 6 mo; 17 had poorer baseline QOL and were lost due to treatment failure  
• SF-36 improvements for antibiotic vs placebo arm were significant (46% vs 18%, p=0.007), but not clear 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) |
| Berende (2016)         | 280 | Patients with persistent Lyme disease symptoms given IV ceftriaxone for 2 wk | Doxycycline or clarithromycin/hydroxychloroquine for 12 wk | Placebo | • SF-36 PCS did not differ between 3 study groups  
• Adverse event rates similar across 3 study groups  
• 4 serious ceftriaxone-related adverse events |

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

**SUMMARY OF EVIDENCE**

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

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

Centers for Disease Control and Prevention
The Centers for Disease Control and Prevention (CDC) currently recommends 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 (EIA) or rarely, an indirect immunofluorescence assay (IFA). 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 EIA or IFA and the immunoblot are both positive. CDC 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 CDC 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 FDA approved.

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

Infectious Diseases Society of America
Practice guidelines on the treatment of Lyme disease, and including discussion of supportive evidence, were issued by the Infectious Diseases Society of America (IDSA) in 2006 and reaffirmed in 2010.

National Guideline Clearinghouse
In January 2016, the National Guideline Clearinghouse (NGC) of the U.S. Department of Health and Human Services removed the IDSA guidelines on Lyme disease. NGC explained that IDSA guidelines were outdated, because there had been no review or revision in 5 years.
European Federation of Neurological Societies
The 2010 European Federation of Neurological Societies (EFNS) guidelines on Lyme neuroborreliosis are similar to the IDSA guidelines and recommend a 14-day course of oral or IV antibiotics in definite or possible acute Lyme neuroborreliosis. In patients with late Lyme neuroborreliosis, a 3-week course of IV antibiotics is recommended. The EFNS guidelines indicated antibiotic use for post-Lyme disease syndrome has shown no effect.

British Infection Association
Similar recommendations can be found in the 2011 British Infection Association’s (BIA) position statement on Lyme disease, which indicates IV antibiotics may be appropriate in Lyme carditis, meningitis, or arthritis for periods of 14 to 21 days. Late neuroborreliosis can be treated with IV antibiotics for 14 to 28 days. BIA’s position statement also notes the use of long-term antibiotics can be harmful.

National Institute for Health and Care Excellence
Guidelines on Lyme disease from the National Institute for Health and Care Excellence are in development. Expected publication date is June 2018.

International Lyme and Associated Diseases Society
The International Lyme and Associated Diseases Society (ILADS) published guidelines in 2014 to address 3 clinical questions: usefulness of antibiotic prophylaxis of tick bites, effectiveness of erythema migrans (EM) treatment, and antibiotic retreatment in patients with persistent symptoms. ILADS noted that the evidence on treatment of tick bites, EM rashes, and persistent manifestations is limited. Regarding the treatment of patients with persistent symptoms, the ILADS panel concluded that the evidence for retreatment is adequate to support retreatment, but is not strong enough to mandate treatment. The panel determined that there was no compelling evidence supporting withholding antibiotics from symptomatic patients, especially since there is a lack of alternative treatment options. Due to the number of clinical variables and the heterogeneity of the patient population, clinical judgment and patients’ values and goals should be considered when planning a treatment strategy.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01163994</td>
<td>Comparison of Ceftriaxone and Doxycycline for Treatment of Multiple Erythema Migrans</td>
<td>500</td>
<td>Oct 2016</td>
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<tr>
<td>Unpublished</td>
<td></td>
<td></td>
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<tr>
<td>NCT01635530</td>
<td>Study of Lyme Neuroborreliosis: Epidemiology, Manifestations, Diagnostics and Treatment</td>
<td>150</td>
<td>May 2016 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
CODING

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

CPT/HCPCS

86617 Antibody; *Borrelia burgdorferi* (Lyme disease) confirmatory test (e.g., Western blot or immunoblot)

87475 Infectious agent detection by nucleic acid (DNA or RNA); *Borrelia burgdorferi*, direct probe technique

87476 Infectious agent detection by nucleic acid (DNA or RNA); *Borrelia burgdorferi*, amplified probe technique (describes PCR technique)

87477 Infectious agent detection by nucleic acid (DNA or RNA); *Borrelia burgdorferi*; quantification

96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

96366 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)

96367 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)

96368 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure)

96374 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug

96375 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of a new substance/drug (List separately in addition to code for primary procedure)

96376 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility (List separately in addition to code for primary procedure)

ICD-9 Diagnoses

049.0 Lymphocytic meningitis

088.81 Lyme disease

323.81 Other causes of encephalitis

323.9 Unspecified cause of encephalitis

350.9 Trigeminal nerve disorder, unspecified

351.0 Bell’s palsy

351.9 Facial nerve disorder, unspecified

352.0 Disorders of olfactory (1st) cranial nerve

352.2–352.6 Disorders of other cranial nerves, code range

352.9 Unspecified disorder of cranial nerves

356.9 Unspecified hereditary and idiopathic peripheral neuropathy (includes polyneuropathy)
Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

377.49 Other disorders of optic nerve
378.51-378.54 Paralytic strabismus code range
388.5 Disorders of acoustic nerve
426.10 Atrioventricular block, unspecified
429.89 Other ill-defined heart diseases (includes Lyme carditis)

ICD-10 Diagnoses (Effective October 1, 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:
- Added to C 1 “in the absence of objective clinical or laboratory evidence for Lyme disease” to read “Patients with symptoms consistent with chronic fatigue syndrome or fibromyalgia, in the absence of objective clinical or laboratory evidence for Lyme disease;”
- Revised in C 9 “>” to “≥” to read, “Patients with chronic (≥6 months) subjective symptoms…”
- Revised in H “Determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment is considered experimental / investigational.” to “Other diagnostic testing is considered experimental / investigational including but not limited to C6 peptide ELISA or determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment.”

Rationale section updated

In Coding section:
- Updated nomenclature for CPT codes: 86617, 87475, 87476, 87477, 96367

References updated
12-07-2012 Description section updated
Rationale section updated
References updated

02-28-2014 In Coding Section:
- ICD-10 Diagnoses codes added

02-01-2017 Description section updated

In Policy section:
- 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:
  - 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..."
REFERENCES


