Name of Policy:
Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

Policy #: 359
Category: Pharmacology
Latest Review Date: January 2014
Policy Grade: C

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Lyme disease (LD) is a multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi* and transmitted by the bite of an infected ixodid tick endemic to Northeastern, North Central, and Pacific coastal regions of the United States. The disease is characterized by stages, beginning with localized infection of the skin (erythema migrans), followed by dissemination to many sites. Manifestations of early disseminated disease may include lymphocytic meningitis, facial palsy, painful radiculoneuritis, atrioventricular nodal block, or migratory musculoskeletal pain. Months to years later, the disease may be manifested by intermittent oligoarthritis, particularly involving the knee joint, chronic encephalopathy, spinal pain, or distal paresthesias. While most manifestations of LD can be adequately treated with oral antibiotics, intravenous (IV) antibiotics are indicated in some patients with neurologic involvement or atrioventricular heart block. However, over diagnosis and overtreatment of LD are common due to its nonspecific symptoms, a lack of standardization of serologic tests, and difficulties in interpreting serologic test results. In particular, patients with chronic fatigue syndrome or fibromyalgia are commonly misdiagnosed as possibly having LD and undergo inappropriate IV antibiotic therapy. The purpose of this policy is to provide diagnostic criteria for the appropriate use of IV antibiotic therapy. The following paragraphs describe the various manifestations of LD that may prompt therapy with IV antibiotics and the various laboratory tests that are used to support the diagnosis of LD.

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 LD, the CSF will show a lymphocytic pleocytosis (lymphocyte count greater than normal) with increased levels of protein. Intrathecal production of antibodies directed at spirochetal antigens is typically present. A normal CSF analysis is strong evidence against Lyme meningitis. Treatment with a two- to four-week course of IV antibiotics, typically ceftriaxone or cefotaxime, is recommended.

Cranial neuritis, most frequently Bell’s palsy, may present early in the course of disseminated LD, occasionally prior to the development of antibodies, such that an LD etiology may be difficult to rule in or out. While Bell’s palsy typically resolves spontaneously with or without treatment with oral antibiotics, some physicians have recommended a lumbar puncture and a course of IV antibiotics if pleocytosis in the CSF is identified, primarily as a prophylactic measure to prevent further neurologic symptoms.

A subacute encephalopathy may occur months to years after disease onset, characterized by subtle disturbances in memory, mood, sleep, or cognition accompanied by fatigue. These symptoms may occur in the absence of abnormalities in the electroencephalogram (EEG), magnetic resonance imaging (MRI), or CSF. In addition, the symptoms are nonspecific and overlap with fibromyalgia and chronic fatigue syndrome. Thus diagnosis of Lyme encephalopathy may be difficult and may be best diagnosed with a mental status exam or neuropsychological testing. However, treatment with IV antibiotics is generally not indicated unless CSF abnormalities are identified.
Much rarer, but of greater concern, is the development of encephalomyelitis, characterized by spastic paraparesis, ataxias, cognitive impairment, bladder dysfunction, and cranial neuropathy. CSF examination reveals a pleocytosis and an elevation in protein. Selective synthesis of anti-spirochetal antigens can also be identified. A course of IV antibiotics with three to four weeks of ceftriaxone is suggested when CSF abnormalities are identified.

A variety of peripheral nervous system manifestations of LD have also been identified. Symptoms of peripheral neuropathy include paresthesias, or radicular pain with only minimal sensory signs. Patients typically exhibit electromyographic (EMG) or nerve conduction velocity abnormalities. CSF abnormalities are usually seen only in those patients with a coexistent encephalopathy.

Cardiac Manifestations of Lyme Disease
Lyme carditis may appear during the early dissemination stage of the disease; symptoms include atrioventricular heart block, tachyarrhythmias, and myopericarditis. Antibiotics are typically given, although no evidence proves that this therapy hastens the resolution of symptoms. Both oral and IV regimens have been advocated. Intravenous regimens are typically used in patients with a high-degree atrioventricular block or a PR interval on the electrocardiogram of greater than 0.3 second. Patients with milder forms of carditis may be treated with oral antibiotics.

Lyme Arthritis
Lyme arthritis is a late manifestation of infection and is characterized by an elevated IgG response to B. burgdorferi and intermittent attacks of oligoarticular arthritis, primarily in the large joints such as the knee. Patients with Lyme arthritis may be successfully treated with a 30-day course of oral doxycycline or amoxicillin, but care must be taken to exclude simultaneous central nervous system (CNS) involvement, requiring IV antibiotic treatment. In the small subset of patients that do not respond to oral antibiotics, an additional 30-day course of oral or IV antibiotics may be recommended.

Fibromyalgia and Chronic Fatigue Syndrome
Fibromyalgia and chronic fatigue syndrome are the diseases most commonly confused with LD. Fibromyalgia is characterized by musculoskeletal complaints, multiple trigger points, difficulty in sleeping, generalized fatigue, headache, or neck pain. The joint pain associated with fibromyalgia is typically diffuse, in contrast to Lyme arthritis, which is characterized by marked joint swelling in one or a few joints at a time, with few systemic symptoms. Chronic fatigue syndrome is characterized by multiple subjective complaints, such as overwhelming fatigue, difficulty in concentration, and diffuse muscle and joint pain. In contrast to LD, both of the above conditions lack joint inflammation, have normal neurological test results, or have test results suggesting anxiety or depression. Neither fibromyalgia nor chronic fatigue syndrome has been shown to respond to antibiotic therapy.

Serologic Tests
The antibody response to infection with B. burgdorferi follows a typical pattern. During the first few weeks after the initial onset of infection, there is no antibody production. The specific IgM response characteristic of acute infection peaks between the third and sixth week. The
specific IgG response develops only after months and includes antibodies to a variety of spirochetal antigens. IgG antibodies produced in response to LD may persist for months or years. Thus, detection of IgG antibodies only indicates exposure, either past or present. In LD endemic areas, underlying asymptomatic seropositivity may range from 5%–10%. Thus, as with any laboratory test, interpretation of serologic tests requires close correlation with the patients’ signs and symptoms. For example, patients with vague symptoms of LD, chronic fatigue syndrome, or fibromyalgia may undergo multiple serologic tests over many weeks to months in an effort to establish the diagnosis of LD. Inevitably, in this setting of repeat testing, one enzyme-linked immunosorbent assay (ELISA) or test, whether IgG or IgM, may be reported as weakly positive or indeterminate. These results most likely represent false positive test results in the uninfected patient who has had long-standing symptoms from a different condition and previously negative test results.

Currently, the Centers for Disease Control and Prevention (CDC) recommend a two-step method for the serologic diagnosis of LD:

1. Enzyme-Linked Immunosorbent Assay (ELISA) for *Borrelia burgdorferi* Antibodies
   This test is a screening serologic test for LD. ELISA tests are available to detect IgM or IgG antibodies or to detect both antibody types together. More recently developed tests using recombinant or synthetic antigens have improved diagnostic sensitivity. For example, the FDA-approved C6 ELISA is highly sensitive to infection, and is under study as an indicator of antibiotic therapy efficacy. A positive or indeterminate ELISA test result alone is inadequate serologic evidence of LD. All of these tests must be confirmed with an immunoblot test. In addition, results must be correlated with the clinical picture.

2. (Western) Immunoblot
   This test is used to confirm the serologic diagnosis of LD in patients with positive or indeterminate ELISA tests. In contrast to the standard ELISA test, the immunoblot investigates the specific antibody response to the different antigens of *B. burgdorferi*. Typically, several clinically significant antigens are tested. According to CDC criteria, the test result is considered positive if two of the three most common IgM antibody bands to spirochetal antigens are present, or five of the 10 most frequent IgG antibody bands are present. Because the CDC criteria were developed for surveillance, they are conservative and may miss true LD cases. Some support the use of more liberal criteria for a positive result in clinical diagnosis; however, alternative criteria have not been well validated. Criteria for interpreting immunoblot results are different in Europe than in the United States due to differences in prevalent *Borellia* species causing disease.

Other tests include:

**Polymerase Chain Reaction (PCR)**
In contrast to the above two serologic tests, which only indirectly assess prior or present exposure to *B. burgdorferi*, PCR directly tests for the presence of the spirochete. Because PCR technology involves amplification of DNA from a portion of *B. burgdorferi*, there is a high risk of exogenous contamination, resulting in false positive results. Positive results in the absence of clear clinical indicators or positive serology are not definitive for diagnosis. In addition, the test cannot distinguish between live spirochetes or fragments of dead ones. The PCR technique
has been studied using a variety of specimens. PCR has the best detection rates for skin biopsies from patients with erythema migrans (but may not be indicated with recent history of tick bite or exposure) and for synovial tissue (and synovial fluid, to a lesser extent) from patients with Lyme arthritis. CSF may be positive by PCR during the first two weeks of infection, but thereafter the detection rate is low. PCR is not recommended for urine or blood specimens. However, PCR-based direct detection of *B burgdorferi* in the blood may be useful for documenting Lyme carditis when results of serologic studies are equivocal.

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

**T-Cell Proliferative Assay**

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

**Evaluation of Cerebrospinal Fluid (CSF)**

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

**Evaluation of the Chemoattractant CXCL13**

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

**Treatment of Lyme Disease**

As noted above, treatment with IV antibiotics is generally indicated only in patients with symptoms and laboratory findings consistent with CNS or peripheral neurologic involvement, and in a small subset of patients with heart block or documented Lyme arthritis who have not responded to oral antibiotics. Typical IV therapy consists of a two- to four-week course of ceftriaxone or cefotaxime, both third-generation cephalosporins, or penicillin or chloramphenicol. No data suggest that prolonged or repeated courses of IV antibiotics are effective. Lack of effect should suggest an incorrect diagnosis or slow resolution of symptoms, which is commonly seen in LD. In addition, some symptoms may persist after treatment, such as Lyme arthritis; this phenomenon may be related to various self-sustaining inflammatory mechanisms rather than persistent infection.
**Policy:**
Treatment of Lyme disease (LD) consists of oral antibiotics, except for the following indications:

A **2- to 4-week course of IV antibiotic therapy meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in patients with neuroborreliosis with objective neurologic complications of documented LD (see the following for methods of documentation).

Objective neurologic findings include:
- Lymphocytic meningitis with documented cerebrospinal fluid (CSF) abnormalities
- Cranial neuropathy, other than uncomplicated cranial nerve palsy, with documented
- Encephalitis or encephalomyelitis with documented CSF abnormalities
- Radiculopathy
- Polyneuropathy

Lyme disease may be documented either on the basis of serologic testing or by clinical findings of erythema migrans in early infection. Documentation of CSF abnormalities is required for suspected CNS infection, as indicated above.

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

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

**Polymerase chain reaction (PCR)-based direct detection of *B. burgdorferi* in CSF samples meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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.

A **2- to 4-week course of IV antibiotics meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in patients with Lyme carditis, as evidenced by positive serologic findings (defined above) and associated with a high degree of atrioventricular block or a PR interval of greater than 0.3 second. Documentation of Lyme carditis may include PCR-based direct detection of *B. burgdorferi* in the blood when results of serologic studies are equivocal.

A **single 2- to 4-week course of IV antibiotic therapy meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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.
**Intravenous antibiotic therapy does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in the following situations:

- Patients with symptoms consistent with chronic fatigue syndrome or fibromyalgia;
- Patients with seronegative LD in the absence of CSF antibodies;
- Initial therapy in patients with Lyme arthritis without coexisting neurologic symptoms;
- Cranial nerve palsy (e.g. Bell’s palsy) without clinical evidence of meningitis;
- Antibiotic-refractory Lyme arthritis (unresponsive to 2 courses of oral antibiotics or to 1 course of oral and 1 course of intravenous antibiotic therapy);
- Patients with vague systemic symptoms without supporting serologic or CSF studies;
- Patients with a positive ELISA test, unconfirmed by an immunoblot or Western blot test (see definition above);
- Patients with an isolated positive serologic test in the setting of multiple negative serologic studies;
- Patients with chronic (> 6 months) subjective symptoms (“post-Lyme syndrome”) after receiving recommended treatment regimens for documented LD.

**Repeat or prolonged courses (greater than 4 weeks) of intravenous antibiotic therapy do not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage.

**Repeat PCR-based direct detection of *B. burgdorferi* does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in the following situations:

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

**PCR-based direct detection of *B. burgdorferi* in urine samples does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in all clinical situations.

**Genotyping or phenotyping of *B. burgdorferi* does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

**Determination of levels of the B lymphocyte chemoattractant CXCL 13 for diagnosis or monitoring treatment does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

**Other diagnostic testing** including but not limited to C6 peptide ELISA does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

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

**Key Points:**

**Direct Detection of B. burgdorferi with PCR Technology**

While diagnosis of Lyme disease (LD) is generally based on the clinical picture and demonstration of specific antibodies, PCR-based technology can detect the spirochete in the CSF in cases of neuroborreliosis, in the synovial fluid of cases of Lyme arthritis, and rarely in skin biopsy specimens of those with atypical dermatologic manifestations. However, a PCR-based test is generally considered a second tier test, performed only when the results of serologic tests and clinical evaluation are equivocal. For example, while PCR-based tests can identify organisms in skin biopsy specimens of patients with dermatologic manifestations (i.e., erythema migrans), this diagnosis is typically made clinically and antibiotic therapy started empirically. A skin biopsy is rarely necessary. Similarly, diagnosis of Lyme arthritis is based on clinical and serologic studies without the need for synovial tissue or fluid. Finally, intrathecal antibody production is considered a more sensitive test than PCR-based CSF detection in patients with suspected neuroborreliosis, but a PCR-based technique may be useful in patients with a short duration of disease (i.e., <14 days) during the window between exposure and the emergence of detectable levels of antibodies in the CSF. However, it should be noted that the test cannot distinguish between live and dead organisms. PCR-based detection is typically not performed in the urine due to the variable presence of endogenous polymerase inhibitors that have an impact on the test's sensitivity.

PCR-based technology has been used as one step in the genotypic analysis of B.burgdorferi. B. burgdorferi was originally characterized as a single species (B. burgdorferi sensu lato), but genotypic analysis has revealed that this group represents three distinct species and genomic groups. Of these, the following have been isolated from patients with LD: B. burgdorferi sensu stricto, B. garinii, and B. afzelii. The prevalence of these different genospecies may vary among populations and may be associated with different clinical manifestations. However, no data were found in the published literature regarding whether or how knowledge of the genotype or phenotype of B. burgdorferi could be used to improve patient management and outcomes. In the U.S., B. burgdorferi sensu stricto is the only human pathogenic species, but in Europe all three species cause infection. Recently a new human pathogenic species, B. spielmanii, was found in a small number of European patients; therefore, criteria for interpreting immunoblot results are different in Europe than in the U.S.

**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. However, data are limited. Additional research is necessary to determine diagnostic and treatment utility. Its use for the diagnosis of Lyme disease or monitoring treatment is considered investigational.
Other Diagnostic Tests
Other diagnostic testing strategies, such as enzyme immunoassay (EIA) using the C6 peptide, have not demonstrated improvements in specificity over the 2-tiered testing approach of ELISA followed by the Western blot. Branda et al reported on the use of whole-cell sonicate EIA (ELISA) followed by C6 EIA and found the specificity and positive predictive values were comparable to the 2-tiered ELISA-Western blot approach (99.5% vs. 98.4%, and 70% vs. 66%, both respectively). Additional research is necessary to determine the validity and interpretation of study results and the value of using the 2-tiered EIA approach over the current standard of EIA (ELISA) followed by Western blot.

Role of Intravenous (IV) Antibiotics
A diagnosis of LD requires appropriate epidemiologic data, supporting clinical observation (including exposure to ixodid ticks in an endemic area), and supporting laboratory findings. However, over-diagnosis and overtreatment of LD is common. Intravenous antibiotic therapy in patients with presumed LD would be inappropriate in the following situations: an incorrect diagnosis; a history of prolonged or repeated courses of IV antibiotics; and use of IV antibiotics when oral antibiotics are adequate. An incorrect diagnosis of LD includes those patients with positive serologies without characteristic signs or symptoms of LD, or those with non-specific symptoms and no known exposure to ticks in an endemic area, or those without supporting serologic evidence.

The evidence generally does not support persistent *B. burgdorferi* infection in patients with well-documented infection who have received recommended antibiotic therapy. Blinded, randomized controlled trials of extended antibiotic therapy versus placebo in such patients have shown no differences in outcomes (summarized in the Table). Moreover, prolonged courses of antibiotic therapy carries a high risk of side effects, including pseudomembranous colitis and the accumulation of ceftriaxone calcium salts in the gall bladder.

While morphologic variants of *B. burgdorferi* have been thought to be related to persistent Lyme disease symptoms, a 2013 systematic review by Lantos and colleagues found no evidence to support this. The reviewers found no pathogenic relationship 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.** Summary of randomized, controlled trials of prolonged antibiotic therapy in patients with well-documented, previously treated Lyme disease

<table>
<thead>
<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>Klemperer et al 2001</td>
<td>78</td>
<td>1) Positive for IgG Abs to <em>B. burgdorferi</em>; persistent symptoms that interfered with patient function</td>
<td>IV ceftriaxone daily for 30 days, oral doxycycline for 60 days</td>
<td>IV and oral placebos</td>
<td>No significant difference in quality of life outcomes for 1) and 2). Studies terminated after interim analysis indicated that it was highly unlikely that a significant difference in treatment efficacy would be observed</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>2) Negative for IgG Abs to <em>B. burgdorferi</em>; else, as above</td>
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Proprietary Information of Blue Cross and Blue Shield of Alabama
Medical Policy #359
<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Patient Description</th>
<th>Intervention and Duration</th>
<th>Placebo Intervention and Duration</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaplan et al 2003</td>
<td>Same trial as Klempner et al 2001</td>
<td>IV ceftriaxone daily for 28 days</td>
<td>IV placebo daily for 28 days</td>
<td>Both treatment and control arms showed similar and not significantly different decreases in Medical Outcomes Study cognitive, pain, and role functioning scales; and improved mood as assessed with the Beck Depression Inventory and Minnesota Multiphasic Personality Inventory</td>
</tr>
<tr>
<td>Krupp et al 2003</td>
<td>Patients with persistent severe fatigue of duration 6 months or longer</td>
<td>IV ceftriaxone daily for 28 days</td>
<td>IV placebo daily for 28 days</td>
<td>Both treatment and control arms showed similar and not significantly different decreases in Medical Outcomes Study cognitive, pain, and role functioning scales; and improved mood as assessed with the Beck Depression Inventory and Minnesota Multiphasic Personality Inventory</td>
</tr>
<tr>
<td>Oksi et al 2007</td>
<td>Consecutive patients treated with standard antibiotic regimen for 21 days</td>
<td>Amoxicillin twice daily for 100 days starting immediately after standard regimen</td>
<td>Placebo twice daily for 100 days starting immediately after standard regimen</td>
<td>Both treatment and control arms showed similar and not significantly different decreases in patient and investigator visual analogue scale (VAS) outcomes (VAS evaluation of symptoms, range 0-100, 0=no symptoms) at 12 mos. B. burgdorferi-specific antibodies declined similarly in both groups over 12 mos.</td>
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<tr>
<td>Fallon et al 2008</td>
<td>Patients with documented objective memory impairment</td>
<td>IV ceftriaxone daily for 70 days</td>
<td>IV placebo daily for 70 days</td>
<td>Primary outcome of cognitive function across 6 domains was similarly improved in both groups at week 24, and was not significantly different between groups; improvement between groups was marginally significantly different at week 12 (p=0.05) Exploratory subgroup analyses suggested significantly better improvement in ceftriaxone-treated patients with more severe baseline pain and physical functioning</td>
</tr>
</tbody>
</table>
Patients with symptoms of arthralgia, cardiac or neurologic involvement with or without fatigue after previous successful antibiotic treatment of Lyme disease; study conducted in a primary care internal medicine practice (52 assigned, 31 evaluable)

Oral amoxicillin 3 gm daily for 3 months (34 assigned, 17 evaluable)

Oral placebo daily for 3 months

--44% of enrolled patients not evaluable at 6 months; 17 of these had poorer baseline quality of life and were lost due to treatment failure --SF-36 improvements for antibiotic vs. placebo arm were significant (46% vs. 18%, p=0.007), but text not clear if analysis of all or only evaluable patients; --SF-36 physical component improvement not significantly different between treatment arms for evaluable patients (8.5 vs. 7); --SF-36 mental component significantly improved in antibiotic arm for evaluable patients (14.4 vs. 6.2, p=0.04)

Summary

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

Diagnostic testing for Lyme disease is challenging and can potentially lead to over-diagnosis and overtreatment. Diagnostic testing may not be necessary when a diagnosis can be made clinically in patients with a recent tick bite or exposure and the presence of the characteristic rash of erythema migrans. When laboratory studies are needed, serologic testing using the two-step ELISA followed by Western blot is the recommended first approach. Polymerase chain reaction (PCR), may be considered medically necessary as a second approach in patients with a short duration of neurologic symptoms (<14 days) or uncertainty in serologic testing. Other uses for PCR-based testing are considered investigational. Genotyping or phenotyping of *B burgdorferi* is considered investigational. Additional research is necessary to determine diagnostic and treatment utility of the CXCL13, and its use is considered investigational. Other diagnostic testing approaches, such as C6 peptide, also warrant additional research and therefore, are considered investigational.

Practice Guidelines and Position Statements

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

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

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

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

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

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

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

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

**Key Words:**
Intravenous Antibiotic Therapy for Lyme Disease, Lyme Disease, Intravenous Antibiotic Therapy

**Approved by Governing Bodies:**
Not applicable

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
CPT Codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>86617</td>
<td><em>Borrelia burgdorferi</em> (Lyme disease) confirmatory test (e.g., Western blot or immunoblot)</td>
</tr>
<tr>
<td>87475</td>
<td>Infectious agent detection by nucleic acid; <em>Borrelia burgdorferi</em>, direct probe technique</td>
</tr>
<tr>
<td>87476</td>
<td>Infectious agent detection by nucleic acid; <em>Borrelia burgdorferi</em>, amplified probe technique (describes PCR technique)</td>
</tr>
<tr>
<td>87477</td>
<td>Infectious agent detection by nucleic acid; <em>Borrelia burgdorferi</em>; quantification</td>
</tr>
</tbody>
</table>
References:


Policy History:
Medical Policy Group, June 2009 (3)
Medical Policy Administration Committee, July 2009
Available for comment July 1-August 14, 2009
Medical Policy Group, January 2011 (3)
Medical Policy Administration Committee, January 2011
Available for comment January 11, 2011 through February 21, 2011
Medical Policy Group, March 2012 (3): Updates to Description, Policy, Key Points, References: Updated Guidelines and “Other Diagnostic Testing” as investigational
Medical Policy Administration Committee, March 2011
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Medical Policy Group, October 2012 (3): Update to Description, Key Points and References
Medical Policy Panel, January 2014
Medical Policy Group, January 2014 (3): Update to Key Points and References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

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