Clinical Policy Title: Lyme disease diagnosis and treatment

Clinical Policy Number: 18.01.05

Effective Date: March 1, 2017
Initial Review Date: February 15, 2017
Most Recent Review Date: February 6, 2018
Next Review Date: February 2019

Related policies:
None.

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of the following services for the diagnosis of Lyme disease to be clinically proven and, therefore, medically necessary:

1. A physical examination of Lyme disease symptoms and physical findings, including rash, facial palsy, and arthritis, plus a history of possible exposure to ticks infected with Lyme disease.

2. Serological blood tests, including enzyme immunoassay (EIA) or immunofluorescence assay (IFA), plus Western immunoblot if either assay is positive or equivocal, when the following conditions are met in the Western immunoblot test. Only U.S. Food and Drug Administration-(FDA-) approved tests are considered medically necessary:
   a. IgM in Western immunoblot — two of the following three bands are present:
      - 21/22/23/24 kDa (OspC).
      - 39 kDa (BmpA).
      - 41 kDa (Fla).
   Or
b. IgG in Western immunoblot -- five of the following 10 bands are present:
- 18 kDa.
- 21/22/23/24 kDa (OspC).
- 28 kDa.
- 30 kDa.
- 39 kDa (BmpA).
- 41 kDa (Fla).
- 45 kDa.
- 58 kDa (not GroEL).
- 66 kDa.
- 93 kDa.

Prestige Health Choice also considers a course of up to 28 days, depending on the particular antibiotic and whether an adult or child is being treated, of a parenteral antibiotic after confirmation of a diagnosis of Lyme disease to be clinically proven and, therefore, medically necessary in accordance with Infectious Diseases Society of America guidelines (CDC, 1995; CDC, 2015a; CDC, 2015b; Wormser, 2006; Wright, 2012).

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.

All other diagnostic tests, including polymerase chain reaction and evaluation of cerebrospinal fluid, tests sometimes used to assist in diagnosing Lyme disease, are considered not medically necessary and, therefore, not covered. Treatment using antibiotics for more than 28 days is not recommended except in cases involving arthritis or neurological symptoms.

Alternative covered services:

None.

Background

Lyme disease is a condition caused by exposure to the bacteria *Borrelia burgdorferi* and *Borrelia mayonii* (in North America). It is transmitted to humans through the bit of an infected tick. Lyme disease has likely existed for centuries, but was first identified in 1975 in the town of Old Lyme, Connecticut. Close to 30,000 new cases per year are reported in the United States, although the actual number is estimated to be 300,000. The disease is most common in New England, the mid-Atlantic region, and a portion of Minnesota and Wisconsin; 95 percent of all reported cases are in 14 states (CDC, 2016a). Infection rates are highest among children ages 5 to 15 and adults over age 50 (Mead, 2015).
Lyme disease is marked by various symptoms; in about 70 percent to 80 percent of cases, a rash that resembles a “bull’s eye” occurs around the site of the tick bite. Within three to 30 days of the bite, symptoms can include fever, chills, headache, fatigue, muscle and joint aches, and swollen lymph nodes. A multiple of other symptoms can present in the months after disease onset in untreated cases (CDC, 2016b). Some cases can be prevented either by applying pesticides to the skin, covering as much of the skin area as possible while in wooded areas, or by removing a recognized tick with tweezers.

If symptoms like those listed above are observed, a physician should be consulted; the physician should review any symptoms and physical findings, and obtain information on recent possible exposures to ticks. The recommended testing procedure includes two steps:

1. Either an Enzyme Immunoassay or an Immunofluorescence assay should be performed. If the test is negative, alternative diagnoses should be considered; if symptoms common in Lyme disease persist for 30 days, a convalescent serum should be considered.
2. If a positive or equivocal result is obtained, and signs and symptoms have been present fewer than 30 days, both an IgG and IgM Western blot should be performed. If the symptoms exceed 30 days, only an IgG Western blot is needed (CDC, 2015a).

Some Lyme disease tests offered by laboratories may not have an established clinical usefulness, including:
- Capture assays for antigens in urine.
- Culture, immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms of *Borrelia burgdorferi*.
- Lymphocyte transformation tests.
- Quantitative CD57 lymphocyte assays.
- “Reverse Western blots.”
- In-house criteria for interpretation of immunoblots.
- Measurements of antibodies in joint fluid (synovial fluid).
- IgM or IgG tests without a previous ELISA/EIA/IFA (CDC, 2015b).

The U.S. Centers for Disease Control and Prevention (CDC) recommends that an IgM Western blot be considered positive for Lyme disease if two of the following three bands are present (21/22/23/24 kDa (OspC); 39 kDa (BmpA); 41 kDa (Fla)). Alternatively, a positive diagnosis can be made if five of the following 10 bands are present on an IgG Western blot (18 kDa; 21/22/23/24 kDa (OspC); 28 kDa; 30 kDa; 39 kDa (BmpA); 41 kDa (Fla.); 45 kDa; 58 kDa (not GroEL); 66 kDa; 93 kDa) (CDC, 1995).

The differentiation of Lyme disease from other disorders has presented a challenge to practitioners. In an early study of 788 patients referred to a Lyme disease clinic at the New England Medical Center in Boston, just 23 percent had active Lyme disease; another 20 percent had previous Lyme disease and another current illness (mostly chronic fatigue syndrome or fibromyalgia); and most of the remaining 57 percent had only chronic fatigue syndrome or fibromyalgia. Prior to referral, 409 of the 788 patients had been treated with antibiotics, and in 322 of these patients, the reason for lack of response was incorrect diagnosis (Steere, 1993).
There are 16 tests for Lyme disease approved by the FDA, all approved from 1987 to 1998 (FDA, 2016). The CDC has warned about the accuracy of tests for Lyme disease that are not FDA approved. One relatively recent method was discussed in the literature, using immunostaining, polymerase chain reaction analysis, and direct DNA sequencing, with 47 percent positive cultures at six days and 94 percent positive at week 16 (Sapi, 2013). The CDC review noted serious concerns about false-positive results caused by lab contamination and potential misdiagnosis using this method (CDC, 2014).

False-positive rates in areas of low endemicity for Lyme disease have been estimated at 2 percent to 5 percent. False negative results when testing occurs within two weeks of infection exceed 50 percent because the test is taken too early for detection (Depietropaolo, 2005).

Treatment of Lyme disease typically involves up to a 28-day course of intravenous parenteral antibiotics. If any symptoms persist after the initial course, tests are typically performed to diagnose any disorders other than Lyme disease.

Efforts have been made to prevent Lyme disease. One such approach is the administration of antibiotics to residents of high-risk geographic areas, especially in the spring and summer months. The effects of such prophylactic approaches are still emerging.

The sole approved vaccine against Lyme disease, developed by SmithKline Beecham, was licensed in 1998 but withdrawn from the market due to limited sales in 2002. Efforts to develop a new vaccine are currently in progress. A successful vaccine could benefit the entire population, as those who have had the disease remain vulnerable to reinfection.

**Searches**

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on December 15, 2017. Search terms were: “Lyme disease” and “Lyme borreliosis.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

Various guidelines for the diagnosis of Lyme disease agree with the CDC-recommended two-tier system of an enzyme immunoassay or immunofluorescence assay, plus an IgG and IgM Western blot (if the assay is positive or equivocal).

The Infectious Diseases Society of America 2006 guideline on Lyme disease recommends treatment with doxycycline for 10–21 days, or amoxicillin or cefuroxime axetil for 14–21 days after initial diagnosis, with smaller doses for children. Re-treatment is recommended only for patients who improve but still have ongoing arthritis or neurological symptoms, for up to four more weeks (Wormser, 2006). The American Academy of Family Physicians guideline agrees with the Infectious Diseases Society of America version (Wright, 2012).

The International Lyme and Associated Diseases Society also has a practice guideline for the treatment of the condition. This guideline supports initial antibiotic treatment of four to six weeks when a rash is present, and also supports continued use of antibiotics if Lyme disease symptoms do not resolve in a relatively short period, as long as the treating physician first discusses the matter with the patient (Cameron, 2014).

Standard treatments for Lyme disease are largely effective short-term, including a Cochrane report of seven studies (n= 450) (Cadavid, 2016). A Hayes report included eight randomized comparative trials, two nonrandomized comparative studies, and two prospective studies of IV antibiotics for late-stage Lyme disease. Cure rates ranged from 28 percent to 81 percent for penicillin, 63 percent to 100 percent for ceftriaxone therapy, and 67 percent to 87 percent for cefotaxime therapy. However, IV therapy was not more effective than oral doxycycline (Hayes, 2014a).

Antibiotics for Lyme disease are largely effective, but do not always resolve patient symptoms. One systematic review of 44 studies found that Lyme neuroborreliosis was detected in 28 percent of patients who completed their treatment (Dersch, 2016). Continued difficulties in explaining the persistence of symptoms in Lyme disease patients beyond the initial treatment period has led to considerable discussion among professionals. In a 2012 statement to the U.S. House of Representatives Foreign Affairs Committee, the Infectious Diseases Society of America stated that, “We sympathize with these patients’ suffering, but remain concerned that a diagnosis of so-called ‘chronic Lyme disease,’ suggesting that active infection is ongoing, is not supported by scientific evidence, and, more alarmingly, the treatment of long-term antibiotic therapy will do patients more harm than good” (ISDA, 2012). The Society accepted comments from the public in 2015 and is now updating its guideline (ISDA, 2016).

A randomized controlled trial (RCT) compared results of a 12-week oral course of doxycycline, clarithromycin plus hydroxychloroquine, or placebo for Lyme disease patients with persistent symptoms.
The SF-36 physical component summary scores were similar for each group at the end of treatment (35.0, 35.6, and 34.8), indicating that long-term antibiotic treatment had no additional effect on the disease (Berende, 2016). A Hayes report of four randomized trials (n=221) found some evidence that long-term use of antibiotics might improve fatigue; conflicting evidence that neurocognitive measures could be improved; and no evidence of improvement of functional status, quality of life, pain, and mood/psychological measures. The report also identified a high rate of treatment-related adverse events, some serious and life-threatening (Hayes, 2014b).

Conversely, a review of four RCTs found improvements in long-term (24-week) treatment with antibiotics in Lyme disease patients. Improvements were found in fatigue, cognitive functioning, physical functioning, and pain (DeLong, 2012).

The accuracy of the two-tier serology approach to diagnose Lyme disease recommended by the CDC has been documented to be relatively high (Steere, 2008) and is given in Table 1:

Table 1
Accuracy of two-tier serology using enzyme-linked immunosorbent assay and Western blot in Lyme disease-endemic area

<table>
<thead>
<tr>
<th>Stage of Lyme disease</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Positive Predictive Value %</th>
<th>Negative Predictive Value %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early localized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute phase</td>
<td>17</td>
<td>98</td>
<td>75</td>
<td>26</td>
</tr>
<tr>
<td>Convalescent phase</td>
<td>53</td>
<td>98</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>Early disseminated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac or neurologic manifestations</td>
<td>100</td>
<td>98</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>Multiple erythema</td>
<td>43</td>
<td>98</td>
<td>89</td>
<td>79</td>
</tr>
<tr>
<td>Late</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis or neurologic manifestations</td>
<td>100</td>
<td>98</td>
<td>94</td>
<td>100</td>
</tr>
</tbody>
</table>

A systematic review and meta-analysis of serological tests in Europe assessed 78 studies on sensitivity to diagnose Lyme disease. Results showed a 50 percent sensitivity for erythema migrans, 77 percent for neuroborreliosis, 97 percent for acrodermatitis chronica atrophicans, and 73 percent for unspecified Lyme borreliosis. The report also found that two-tier antibody indices did not outperform single-test approaches (Leeflang, 2016). Another systematic review of 18 studies found a 59.5 percent overall sensitivity, varying from 62.4 percent for Western blot kits, 62.3 percent for enzyme-linked immunosorbent assay tests, 53.9 percent for synthetic C6 peptide ELISA tests, and 53.7 percent when the two-tier method was used. Sensitivity had improved only 4 percent in the past two decades (Cook, 2016).
A systematic review and meta-analysis of 48 studies of diagnostic tests for Lyme disease concluded that the Immunetics® C6 B. burgdorferi ELISA™ and the two-tier approach have superior specificity compared to potential replacements, and the Western blot algorithm is equally or more specific than other proposed test algorithms. Test sensitivity with progression of *B. burgdorferi* infection is observed from early to late Lyme disease (Waddell, 2016).

False-positive results when testing for Lyme disease remain a concern. One study found 50 of 182 patients (27.5 percent) referred to an infectious disease physician for possible Lyme disease were found to have a false-positive IgM immunoblot, and 78.0 percent of these had received unnecessary antibiotic therapy (Seriburi, 2012).

Reports show that most persons promptly diagnosed and treated with a course of antibiotics up to 28 days will recover completely. Mortality from Lyme disease as an underlying cause of death is rare (Kugeler, 2011). There is, however, a minority of patients, estimated at between 2 percent and 40 percent, who continue to experience fatigue, musculoskeletal, or neurocognitive symptoms after treatment. The term “post-treatment Lyme disease syndrome” is now commonly used among providers. Early studies put the figure of post-treatment Lyme disease syndrome at 34 percent (Shadick, 1994) and 62 percent (Asch, 1994).

In 2005, the Swiss Society of Infectious Diseases published a case definition for post-treatment Lyme disease syndrome, and an update was published in 2015. The guidelines emphasize the growing body of literature that document prolonged or repeated antibiotic therapy is not beneficial and thus contraindicated, and recommend cognitive behavioral therapy and low-impact aerobic exercise (Nemeth, 2016). A U.S. guideline for post-treatment Lyme disease syndrome was included in a 2006 report by the Infectious Diseases Society of America (Wormser, 2006).

One theory is that post-treatment Lyme disease syndrome and chronic fatigue syndrome may be part of the same disorder, as symptoms are similar. However, a 2015 study found that 49.4 percent of post-treatment Lyme disease syndrome patients had a significantly increased level and frequency in IgG anti-neural antibody reactivity, while chronic fatigue syndrome patients had only a 7.8 percent reactivity rate, similar to the 13.2 percent rate in healthy controls (Ajamian, 2015).

Along with the efforts to understand post-treatment Lyme disease syndrome, research has identified at least one new genetic form of Lyme disease, namely *Borrelia mayonii*. Mayo Clinic researchers found six samples from Minnesota, Wisconsin, and North Dakota that contained DNA of this new species, five through blood samples and the other through synovial fluid, that had classic symptoms of Lyme disease (Pritt, 2016).

Another potential form of Lyme disease is that of *Borrelia bissettii*. Historically, this spirochete has been associated only with European cases of Lyme disease; however, researchers found that in 27 northern California patients with Lyme borreliosis, three of them showed evidence of infection with an organism closely related to *Borrelia bissettii* (Girard, 2011). A later study of samples in Georgia and Florida also showed a close relationship with *Borrelia bissettii* (Golovchenko, 2016).
A meta-analysis of four placebo-controlled trials (n=1,082) that administered prophylactic antibiotics to prevent Lyme disease in high-risk geographic areas found risk in the placebo group was 2.2 percent, compared with 0.2 percent in the treated group, a significant reduction. Authors conclude that one case of Lyme disease was prevented for each 50 patients given prophylaxis (Warshafsky, 2010).

While there is no accepted vaccine against Lyme disease, various tests are now being performed. Phases I and II of clinical trials of a novel multivalent OspA vaccine in healthy adults previously infected with *Borrelia burgdorferi* have been reported as well tolerated and effective in inducing antibodies (Wressnigg, 2014). A meta-analysis found that multivalent vaccines had much lower rates of symptoms than did monovalent vaccines (6.8 times fewer cases of redness, 2.9 times fewer cases of fever). Other rates of local and systemic adverse events were non-significantly lower for multivalent vaccines. The prevention of Lyme disease for monovalent vaccines was 60 percent lower, an odds ratio of 0.40, significant at p<0.005 (Badawi, 2017).

Policy updates:

A total of three guidelines/other and three peer-reviewed references were added and one peer-reviewed reference was removed from this policy in December 2017.

### Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Cook (2016)</td>
<td>Sensitivity comparison of types of Lyme borreliosis tests</td>
</tr>
<tr>
<td></td>
<td>Key points:</td>
</tr>
<tr>
<td></td>
<td>• Meta-analysis of 18 studies samples proven to be positive for Lyme using serology tests, evidence of erythema migrans rash, and/or culture.</td>
</tr>
<tr>
<td></td>
<td>• Weighted mean sensitivity for all tests was 59.5 percent.</td>
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<tr>
<td></td>
<td>• Sensitivities ranged from 62.4 percent (Western blot), 62.3 percent (enzyme-linked immunosorbent assay tests), 53.9 percent (synthetic C6 peptide ELISA tests), to 53.7 percent when two-tier method was used.</td>
</tr>
<tr>
<td></td>
<td>• Sensitivity has only risen 4 percent over 20-year study period.</td>
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</table>

| Dersch (2016)             | Patients with continued Lyme neuroborreliosis after standard treatment |
|---------------------------|Key points:                        |
|                           | • Systematic review of 44 studies of diagnosed Lyme disease after standard treatment. |
|                           | • Patients followed from seven days to 20 years after treatment. |
|                           | • Weighted mean proportion of patients with residual symptoms after initial therapy was 28 percent. |
|                           | • Authors conclude that the persistence of fatigue and cognitive impairment (post-Lyme syndrome) could be an artifact of unspecific case definitions in single studies. |

| Wressnigg (2014)          | Safety and immunogenicity trials of vaccine against Lyme borreliosis |
|---------------------------|Key points:                        |
|                           | • Randomized phase I/II trial of a novel multivalent OspA vaccine in healthy adults, either seropositive or seronegative for previous *Borrelia burgdorferi* infection. |
|                           | • Participants given three monthly priming immunizations, and a booster either six months or nine to 12 months later. |
|                           | • ELISA and surface binding antibody responses against all six OspA antigens were induced in both populations. |
|                           | • Adverse events were predominantly mild and transient. |

| Warshafsky (2010)         | Key points:                        |
Efficacy of prophylactic antibiotics in high risk areas for Lyme disease

- Systematic review/meta-analysis of four clinical trials (n=1,082).
- Lyme disease in placebo group was 2.2 percent, 0.2 percent for prophylactic group.
- One case of Lyme disease prevented for every 50 patients treated with antibiotics.

References

Professional society guidelines/other:


U.S. Centers for Disease Control and Prevention (CDC). Notice to Readers Recommendations for Test Performance and Interpretation from the Second National Conference on Serologic Diagnosis of Lyme


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.
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<th>CPT code</th>
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<tr>
<td>86617</td>
<td>Borrelia burgdorferi (Lyme Disease) confirmatory test (e.g., Western blot or immunoblot)</td>
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<table>
<thead>
<tr>
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<td>A69.22</td>
<td>Other neurological orders in Lyme disease</td>
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<td>A69.23</td>
<td>Arthritis due to Lyme disease</td>
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<td>Other conditions associated with Lyme disease</td>
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<table>
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