Lyme Disease

Laboratory Support of Diagnosis and Management

CLINICAL BACKGROUND

Lyme disease or Lyme borreliosis is by far the most common tick-borne disease in the United States. It is caused by the bacterium *Borrelia burgdorferi* and transmitted from the deer tick (*Ixodes scapularis* or *Ixodes pacificus*). In 2023, approximately 90,000 cases of Lyme disease were reported to the CDC by healthcare providers[1] but, based on insurance claims data, the annual number of patients diagnosed and treated could be as high as 476,000 per year.[2]

Lyme disease cases are most frequently reported from the upper midwestern, northeastern, and Mid-Atlantic states.[3] However, cases are also reported from Northern California, Oregon, and Washington. Lyme disease is most common among children and middle-aged adults.[4]

The clinical presentation of Lyme disease is categorized as 1 of 3 stages: early localized, early disseminated, and late (**Table 1**).[3,5-7] In 70% to 80% of infected persons, early localized disease is characterized by erythema migrans (EM), a round skin lesion at least 4 cm to 5 cm in diameter that may appear in a "bulls-eye" pattern and expand up to 30 cm across.[3] In the absence of EM, the differential diagnosis may include other tick-borne diseases such as hard tick relapsing fever (*Borrelia miyamotoi* disease), which is often misdiagnosed as Lyme disease owing to overlapping symptoms.[8]

The first sign of early disseminated disease is often additional smaller skin lesions that may develop if Lyme disease is untreated; however, a recognized skin lesion does not always occur. Extracutaneous involvement in early disseminated disease can include cardiac, rheumatologic, and/or neurologic manifestations (**Table 1**).[3,5-7] About 10% to 15% of patients with untreated Lyme disease will develop Lyme neuroborreliosis (LNB).[9] Lyme arthritis may also occur during late-stage disease and is the most common manifestation of Lyme disease months after initial tick exposure.[10] Left untreated, Lyme arthritis usually affects the knees over a period of several years.[10]

If initiated in the early stages of Lyme disease, treatment with appropriate antibiotics is usually effective.[7] Prophylaxis or serologic testing after a tick bite is usually not indicated in areas where less than 20% of ticks are infected; however, in areas where infected ticks are endemic, laboratory testing, including tick identification, is recommended.[7]

This Clinical Focus provides information on appropriate test selection and interpretation in patients with suspected Lyme disease. The information in the text and tables is provided for informational purposes only and is not intended as medical advice. Test selection and interpretation, diagnosis, and patient management decisions should be based on the physician's education, clinical expertise, and assessment of the patient.

INDIVIDUALS SUITABLE FOR TESTING

- Symptomatic (**Table 1**) individuals with a history of exposure to a tick-endemic area

TEST AVAILABILITY

Laboratory tests that can help confirm the clinical diagnosis of Lyme disease include tick identification, various serologic techniques and polymerase chain reaction (PCR)-based assays (**Table 2**). Panel components may be ordered individually.

TEST SELECTION AND INTERPRETATION

A timeline of tick exposure in a tick-endemic area and symptoms of Lyme disease guide appropriate test selection (**Table 1**).[3,5-7] Guideline recommendations include testing for IgM and/or IgG antibodies using either standard 2-tiered testing (STTT, test code 6646) or modified 2-tiered testing (MTTT, test code 39733)[6,7,11]; in MTTT, second-tier testing is performed by a second enzyme immunoassay instead of a Western blot. MTTT detects up to 30% more cases compared to STTT in patients with early Lyme disease.[12,13] The sections below outline appropriate test selection based on the stage of disease along with characteristic test results.

Early localized Lyme disease

Diagnosis of early localized Lyme disease can sometimes be made on the basis of EM alone without laboratory testing.[3] Importantly, serologic testing during the acute phase of Lyme disease is less sensitive than at later stages of disease.[6] When testing is done too soon (≤14 days) following infection, negative or equivocal results may occur due to the time needed for the immune system to develop a serologic response.[6] Positive or repeat testing (test codes 29477, 8593) on another sample collected in 7 to 14 days is recommended.[6] Serologic testing (MTTT or STTT) may also be considered in patients with 1 or more skin lesions suggestive of, but atypical for, EM.[7]

If first-tier testing performed 14 days after suspected infection is negative, then second-tier testing is not required.[6] If first-tier testing is positive or equivocal, then second-tier testing is required.[6] For samples collected from patients with symptoms lasting 30 days or less, positive IgM is consistent with infection regardless of IgG seropositivity.[6]

Table 1. Lyme Disease: Stages, Symptoms, and Recommended Laboratory Testing

Stage of disease[3,5]	Symptom onset[3]	Symptoms[3]	Laboratory testing[3,7]
Early localized (acute phase)	3-30 days after tick bite	• EM • Fever, myalgia, headache, nausea, fatigue	If EM is identified in a patient where Lyme disease is endemic, serologic testing is not recommended (ie, clinical diagnosis of Lyme is recommended) STTT or MTTT may be considered (weakly recommended) for patients with 1 or more skin lesions suggestive of but atypical for EM; however, serologic testing during the acute phase of infection is less sensitive and specific than testing at later stages of infection
Early disseminated	3-12 weeks after tick bite	• Dermatologic: multiple EM rashes that are distant from bite • Neurologic: LNB – common symptoms include Bell's palsy, lymphocytic meningitis, painful radiculoneuritis (1 or more dermatomes), and others such as painful peripheral motor and sensory neuropathy (mononeuritis multiplex) and intracranial hypertension (rare) • Cardiac: Lyme carditis leading to conduction abnormalities such as AV node block; can be fatal (rare) • Rheumatologic: transient and/or migratory arthritis; effusion in 1 or more joints, often large joints; Baker's cysts; migratory pain in tendons, bursae, muscle, and bones	When assessing for possible LNB affecting either the PNS or CNS, STTT or MTTT, serum is recommended If LNB or 1 or more acute symptoms (eg, meningitis, painful radiculoneuritis) of LNB is suspected, guideline recommendations include obtaining simultaneous samples of CSF and serum for measuring CSF:serum antibody index STTT or MTTT is recommended when assessing for rheumatologic symptoms of Lyme disease; PCR is recommended in seropositive patients
Late-stage	Months to years after tick bite	• Patients may not have a history of EM; however, may present with sensory axonal polyneuropathy, encephalomyelitis (rare), or mononeuropathy • Cognitive deficits, personality changes, extreme irritability, and depression • Lyme arthritis • Bluish red rash (acrodermatitis chronica atrophicans) in women	STTT or MTTT is recommended with IgG only considered >30 days after symptom onset

CNS, central nervous system; CSF, cerebrospinal fluid; EM, erythema migrans; LNB, Lyme neuroborreliosis; MTTT, modified 2-tiered testing; PCR, polymerase chain reaction; PNS, peripheral nervous system; STTT, standard 2-tiered testing.

Early disseminated Lyme disease

Two-tiered testing is recommended when clinical findings are suggestive of early disseminated Lyme disease (**Table 1**).[3,5-7] For specimens collected at 2 to 4 weeks after onset of symptoms, 2-tiered testing that is positive for IgM and negative for IgG indicates early infection, unless obtained on a specimen collected more than 1 month after onset of symptoms.[6] If the specimen was collected more than 1 month after onset of symptoms, a positive IgM finding is more likely to represent a false-positive result unless IgG is also positive; vaccination or other diseases may also cause false-positive results.[6] A positive IgG result by 2-tiered testing is required to confirm the diagnosis of early disseminated Lyme disease but it does not differentiate between active and past *B burgdorferi* infection.[3,14]

A diagnosis of LNB involving either the peripheral nervous system or central nervous system (CNS) can be supported if *Borrelia* antibody or DNA are detected in serum or cerebrospinal fluid (CSF); however, serum antibody testing is recommended over PCR due to low clinical sensitivity (38%).[7,15] If LNB involving the CNS is suspected and CSF testing is performed, a validated laboratory method for the determination of the CSF:serum antibody index using simultaneously obtained CSF and serum samples is recommended.[7] The antibody levels in the CSF that are compared to control levels (ie, serum antibody or albumin) in the CSF:serum antibody index can be measured by enzyme-linked immunosorbent assay (ELISA) or nephelometry (test code 34194); an elevated antibody index strongly supports a diagnosis of LNB.[16]

Table 2. Tests Available for Diagnosis and Management of Lyme Disease

Test code	Assay[a] (component test code)	Method	Clinical use
39209	*Borrelia burgdorferi* DNA, Qualitative Real-Time PCR, Miscellaneous[b,c]	Real-time PCR	Diagnose Lyme disease using whole blood, synovial fluid, or CSF
39684	*Borrelia miyamotoi* Antibody (IgG, IgM), Immunoassay[b]	Immunoassay	Differentially diagnose *B miyamotoi* disease vs Lyme disease
93795	*Borrelia miyamotoi* DNA, Qualitative Real-Time PCR, Miscellaneous[a]	Real-time PCR	Confirm diagnosis of *B miyamotoi* disease
15777	*Borrelia Species* DNA, Qualitative Real-Time PCR, Miscellaneous[b]	Real-time PCR	Detect *Borrelia* spp DNA in whole blood, synovial fluid, or CSF
15510	*Borrelia* Species DNA, Qualitative Real-Time PCR, Tick[b]	Real-time PCR	Detect *B burgdorferi* in tick to assess risk of Lyme disease
32919	*Borrelia* Species DNA, Real-Time PCR, With Reflexes, Blood[c,d]	Real-time PCR	Detect *Borrelia* spp DNA; diagnose Lyme disease or *B miyamotoi* disease in whole blood
39218	*Borrelia* Species DNA, Real-Time PCR, With Reflexes, Synovial Fluid/CSF[c,d]	Real-time PCR	Detect *Borrelia* spp DNA; diagnose Lyme disease or *B miyamotoi* disease in synovial fluid or CSF
6646	Lyme Disease Ab With Reflex to Blot (IgG, IgM)[d]	Immunoassay	Diagnose Lyme disease by standard 2-tiered test
39733	Lyme Disease Antibody With Reflex to Immunoassay (IgG, IgM)(MTTT)[d] Includes reflex to Lyme disease supplemental antibodies (IgG, IgM) if Lyme disease antibody is positive or equivocal.	Immunoassay	Diagnose Lyme disease by modified 2-tiered test
34194	Lyme Disease Antibody Index for CNS Infection	ELISA; Nephelometry	Diagnose Lyme neuroborreliosis
8593	Lyme Disease Antibodies (IgG, IgM), Immunoblot	Immunoblot	Diagnose Lyme disease when ELISA results are positive or equivocal
29477	Lyme Disease Antibody (IgG), Immunoblot		
94322	Tick-borne Disease, Acute Molecular Panel Includes *Anaplasma phagocytophilum* (17320), *Babesia microti* (37314), *Borrelia miyamotoi* (93795), *Ehrlichia chaffeensis* (11353), and Lyme disease *Borrelia* spp (15777).	Real-time PCR	Diagnose tick-borne diseases when selecting tests for individual pathogens is challenging owing to overlapping geographic distributions and clinical presentations of illness; especially useful to diagnose mixed infections
16220	Tick-borne Disease, Antibody Panel With Reflexes[b,d] Includes Lyme disease Ab with reflex to immunoassay (IgG, IgM, 39733) and *A phagocytophilum* antibodies (IgG and IgM, 16189); *B microti* antibodies (IgG and IgM, 16194); and *E chaffeensis* (IgG and IgM, 16197) with reflexes to titers.	IFA	Diagnose tick-borne diseases when selecting tests for individual pathogens is challenging owing to substantial clinical overlap and coinfection
90558	Tick ID With Reflex to Lyme Disease DNA, Real-Time PCR, Tick[d]	Microscopy; reflex to PCR	Identify tick and *B burgdorferi* to assess risk of tick-borne disease and assist with differential diagnosis

CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; PCR, polymerase chain reaction.

[a] Panel components may be ordered individually.

[b] This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

[c] Please refer to the Quest Test Directory for your service area for test availability.

[d] Reflex tests are performed at an additional charge and are associated with an additional CPT® code(s).

Negative serology results may indicate lack of infection or lack of seroconversion, which may occur if samples are collected too early after disease onset or when early antibiotic therapy blunts the antibody response.[6] PCR-based assays (test codes 94322, 39209, 15777, 39219, 39218, 15510, 90558) can be useful in the workup of *B burgdorferi* infection if seroconversion has not yet occurred; these assays, however, are limited by low clinical sensitivity (18%).[17] Untreated patients who continue to be symptomatic for months or years but are IgG-negative are unlikely to have Lyme disease, and a differential diagnosis should be considered.[7]

Late-stage Lyme disease

In patients with suspected Lyme disease that has been left untreated for months to years after a tick bite, symptoms that are characteristic of late-stage disease such as Lyme arthritis or LNB can help guide diagnostic test selection. Detection of *Borrelia* DNA in synovial fluid, commonly from the knees, supports the diagnosis of Lyme arthritis (sensitivity, 78%; specificity, 100%).[10,17]

Differential diagnosis

In addition to clinical presentation and microscopy, hard-tick relapsing fever (*Borrelia miyamotoi* disease) (HTRF [BMD]) can be distinguished from Lyme disease by serology (test code 39684) and molecular testing.[3] Negative serology results do not rule out HTRF (BMD) infection and may be due to testing prior to seroconversion during the acute phase of infection.[18] PCR amplification of *B miyamotoi* DNA (test code 93795) is part of an acute molecular panel of tests (94322) used to confirm a presumptive diagnosis of HTRF (BMD).

See TestDirectory.QuestDiagnostics.com/Test/Test-Guides/TB_Tick-borneDis/ for more details on HTRF (BMD) and information on differential diagnoses of other tick-borne diseases.

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