Tick-borne Diseases

Laboratory Support of Diagnosis and Management

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CLINICAL BACKGROUND

Tick-borne diseases are caused by infections transmitted to humans via a tick vector such as the deer tick, dog tick, wood tick, or lone star tick. Causative agents include bacteria, viruses, parasites, and protozoa. The incidence varies by geographic location and causative agent **(Table 1)**.[1-4] Clinical manifestations also vary depending on the causative agent but frequently include fever, chills, sweating, headaches, myalgia, arthralgia, nausea, and vomiting; because of similar symptomology, tick-borne diseases have substantial clinical overlap.[2,5-10] Some patients develop a rash or lesion at the site of the bite. More severe disease may lead to hematologic, respiratory, cardiac, and neurologic complications, as well as kidney or liver failure and arthritis. Although tick-borne illnesses can be fatal, antimicrobial agents are usually effective for bacterial tick-borne diseases. Some ticks can harbor more than 1 infectious agent (eg, *Borrelia burgdorferi* and *Babesia microti*) that can be transmitted to humans, and coinfection may complicate the diagnosis and affect treatment selection.[11,12]

Preliminary differential diagnosis is primarily based on clinical presentation and a history of exposure in areas where vector ticks are endemic **(Figure)**. In symptomatic patients, a rash or lesion may provide the first clue to the diagnosis; however, absence of a rash should not rule out a condition from the differential diagnosis. Identification of the tick is recommended by the Infectious Diseases Society of America (IDSA), as some disease pathogens are carried by specific tick species. Because of rapid disease progression associated with some tick-borne infections (eg, Lyme disease, tick-borne rickettsial diseases [TBRDs]), treatment should not be delayed pending the results of laboratory tests or the development of more serious symptoms.[13-15]

Lyme Disease

Lyme disease is by far the most common tick-borne disease in the United States. It is caused by the bacterium *B burgdorferi* and transmitted from the deer tick (*Ixodes scapularis* or *Ixodes pacificus*). Since 2008, approximately 30,000 to 40,000 cases of Lyme disease have been reported to the Centers for Disease Control and Prevention (CDC) every year, with most cases occurring during the summer months.[16] In 2019, approximately 35,000 confirmed and probable cases of Lyme disease were reported by healthcare providers[17]; however, insurance records suggest a higher incidence.[18]

Table 1. Incidence of Tick-borne Diseases, United States[1-4]

Disorder (reported cases, 2019)	Causative organism	Primary vector tick(s)	US geographic distribution[a]
Lyme disease (34,945)	*Borrelia burgdorferi, Borrelia mayonii*	Black-legged tick, also known as deer tick (*Ixodes scapularis*)	Northeast[b], Mid-Atlantic[b], upper Midwest[b]
		Western black-legged tick (*Ixodes pacificus*)	Pacific Coast, Northern California
Anaplasmosis/ Ehrlichiosis (7,976)			
Anaplasmosis, also known as human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	Black-legged tick, also known as deer tick (*Ixodes scapularis*)	Upper Midwest, Northeast
		Western black-legged tick (*Ixodes pacificus*)	Pacific Coast of Northern California
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	Lone star tick (*Amblyomma americanum*)	Southeast, Northeast
		American dog tick (*Dermacentor variabilis*)	East of the Rocky Mountains, Pacific Coast
Human ehrlichiosis ewingii	*Ehrlichia ewingii*	Lone star tick (*Amblyomma americanum*)	Southeast, East
Ehrlichia muris eauclairensis (formerly *Ehrlichia muris*-like agent) ehrlichiosis	*Ehrlichia muris eauclairensis*	Black-legged tick, also known as deer tick (*Ixodes scapularis*)	Wisconsin
Spotted fever rickettsiosis (5,207)	*Rickettsia rickettsii* (RMSF)	American dog tick (*Dermacentor variablis*)	East of the Rocky Mountains, Pacific Coast
	Rickettsia parkeri	Rocky Mountain wood tick (*Dermacentor andersoni*)	Rocky Mountain states
	Rickettsia philipii	Pacific Coast tick (*Dermacentor occidentalis*)	California
Babesiosis (2,420)	*Babesia microti* and other *Babesia* species	Black-legged tick, also known as deer tick (*Ixodes scapularis*)	Upper Midwest, Northeast
		Western black-legged tick (*Ixodes pacificus*)	Pacific Coast of Northern California
Tularemia (274)	*Francisella tularensis*	Lone star tick (*Amblyomma americanum*)	Southeast, East
		Rocky Mountain wood tick (*Dermacentor andersoni*)	Rocky Mountain states
		American dog tick (*Dermacentor variabilis*)	East of the Rocky Mountains, Pacific Coast

(Continued)

Table 1. Incidence of Tick-borne Diseases, United States[1,2] *(Continued)*

Disorder (reported cases, 2019)	Causative organism	Primary vector tick(s)	US geographic distribution[a]
Powassan virus neuroinvasive disease/ encephalitis (43)	*Flavivirus*	Black-legged tick, also known as deer tick (*Ixodes scapularis*)	Northeast, Virginia, Wisconsin
Colorado tick fever (59[c])	Colorado tick fever virus	Rocky Mountain wood tick (*Dermacentor andersoni*)	Rocky Mountain states
***Borrelia miyamotoi* disease (unknown)**	*Borrelia miyamotoi*	Black-legged tick, also known as deer tick (*Ixodes scapularis*)	Upper Midwest, Northeast
		Western black-legged tick (*Ixodes pacificus*)	Pacific Coast of Northern California
Heartland and Bourbon virus diseases (unknown)	Heartland virus, Bourbon virus	Lone star tick *(Amblyomma americanum)*	Midwest, South
Tick-borne relapsing fever (unknown)	*Borrelia hermsii*	*Ornithodoros* species	West

RMSF, Rocky Mountain spotted fever.
[a] See reference 1 for detailed geographic distribution maps.
[b] In 2019, the incidence of Lyme disease was high in these regions of the United States.[1]
[c] Cases were reported to the CDC from 2010 through 2019.[3]

Lyme disease cases are heavily centered in New England and the Mid-Atlantic.[16,19] However, they are also found in Wisconsin and Minnesota and, to a lesser extent, in other states in the Great Lakes region and in Pacific Coastal regions. Lyme disease is most common among children and middle-aged adults.[20]

The clinical presentation of Lyme disease is categorized as 1 of 3 stages: early localized, early disseminated, and late **(Table 1)**.[11,12,20-25] In 70% to 80% of infected persons, early localized disease is characterized by erythema migrans (EM), a round or oval skin lesion at least 4 to 5 cm in diameter that may appear in a "bulls-eye" pattern and expand up to 30 cm across.[26] In the absence of EM, the differential diagnosis may include other tick-borne diseases such as *Borrelia miyamotoi* disease (BMD), which is often misdiagnosed as Lyme disease owing to overlapping symptoms.[27]

The first sign of early disseminated disease is often additional smaller 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 the musculoskeletal, cardiac, or nervous systems.

In late-stage disease, Lyme carditis may overlap temporally with Lyme neuroborreliosis, a neurologic manifestation marked by symptoms such as cognitive impairment and memory difficulties.[28] About 10% to 15% of patients with untreated Lyme disease will develop Lyme neuroborreliosis.[28] Lyme arthritis may also occur during late-stage disease and is the most common manifestation of Lyme disease months after initial tick exposure.[29] Left untreated, Lyme arthritis usually affects the knees over a period of several years.[29]

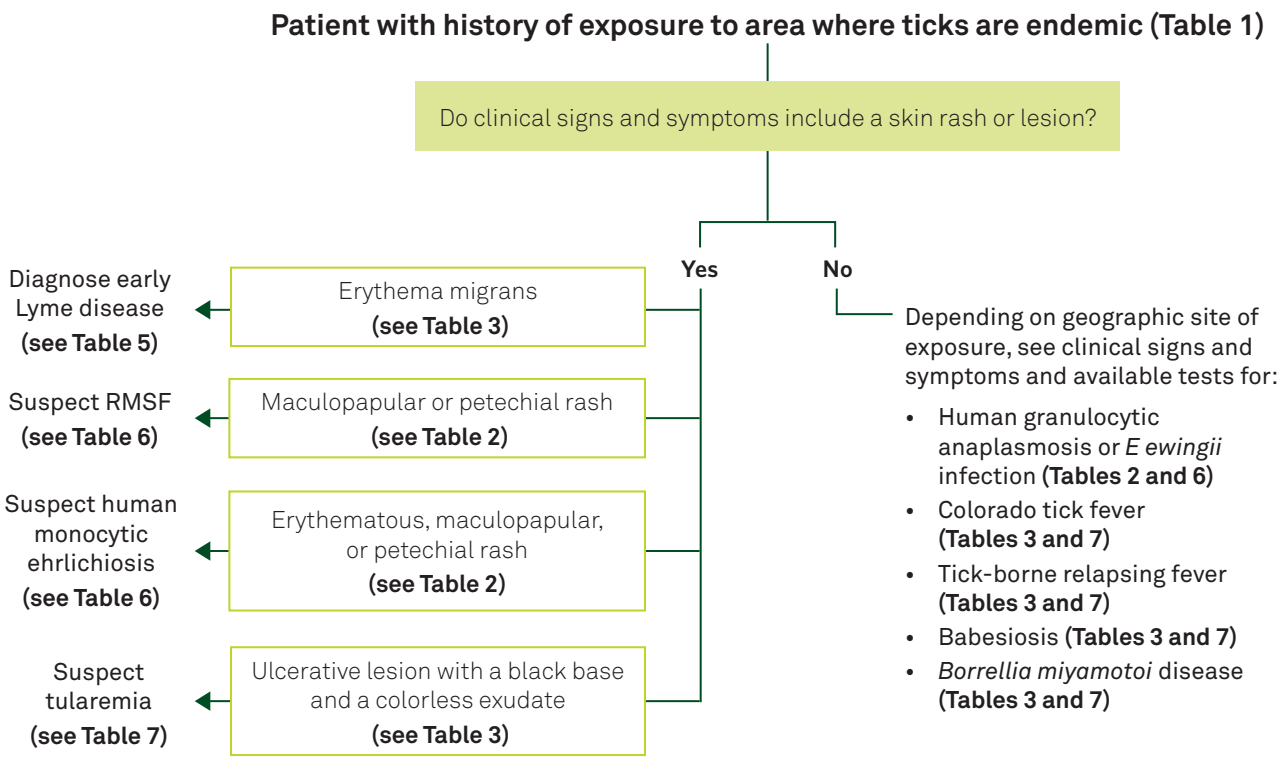
If initiated in the early stages of Lyme disease, treatment with appropriate antibiotics is usually effective.[11,30] Prophylaxis or serologic testing after a tick bite is usually not indicated in areas where less than 20% of ticks are infected; however, in areas where infected ticks are endemic, laboratory testing, including tick identification, is recommended.[11,30]

Tick-borne Rickettsial Diseases

TBRDs include spotted fever rickettsiosis (SFR), human monocytic ehrlichiosis (HME) and other ehrlichioses, and anaplasmosis including human granulocytic anaplasmosis (HGA). TBRDs commonly manifest with an acute onset of nonspecific symptoms that mimic benign viral infections, making diagnosis difficult **(Table 2)**.[2,5-10] The presence or absence of a rash can be a useful diagnostic aid.

Because antibiotic treatment is most effective when given early, therapy for symptomatic patients with clinically suspected TBRDs should not be delayed pending confirmatory laboratory results.[13,14] Once the presumptive diagnosis of

Figure. An Approach to the Differential Diagnosis of Tick-borne Diseases



RMSF, Rocky Mountain spotted fever.

A maculopapular or petechial rash may be present in up to 15% of patients with Colorado tick fever. Rash may be present in 18% of patients with tick-borne relapsing fever.[51]

This figure was developed by Quest Diagnostics. It 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.

TBRD is made based on endemic exposure and clinical signs and symptoms, doxycycline is generally the drug of choice for both children and adults.[5,13,14]

Spotted Fever Rickettsiosis

SFR includes Rocky Mountain spotted fever (RMSF), and *Rickettsia parkeri* and *Rickettsia philipii* rickettsioses; in very rare cases, SFR can be caused by *Rickettsia conorii* infection and is usually identified in people returning from international travel to endemic areas.[31] SFR has been reported from each of the 48 contiguous states and the District of Columbia, although 5 states (Arkansas, Missouri, North Carolina, Tennessee, and Virginia) accounted for more than 50% of cases in 2018.[32] The peak season for infection coincides with tick activity level for the region, but infection has been reported throughout the year.[32] The reported incidence has increased in recent decades to about 13 cases per million population in 2015.[32] This increase in incidence has been accompanied by a decrease in case fatality rate, to 0.1% in 2015.[32] Although infection is most common in the 60- to 64-year-old age group, children younger than 10 years have the highest case-fatality rate.[32]

RMSF, the most severe of the rickettsial illnesses, is caused by *Rickettsia rickettsii*. This organism infects endothelial cells and causes small-vessel vasculitis that usually results in a maculopapular or petechial rash. Symptoms tend to appear 3 to 12 days after a bite. RMSF is also the most severe of the rickettsioses in the United States. Vasculitis in organs such as the brain or lungs can lead to life-threatening complications.

Table 2. Clinical Features of Tick-borne Rickettsial Diseases[2,5-10]

Disease	Incubation period, days	Signs and symptoms	Rash
Rocky Mountain spotted fever	3-12	Fever, headache, malaise, myalgia, edema around eyes and back of hands, nausea/vomiting	Maculopapular rash 2-5 days after fever onset in 50%-80% of adults and >90% of children; frequently on palms and soles
Rickettsia parkeri rickettsiosis	2-10	Fever, headache, muscle aches	Eschar (dark scab), usually days to a week after the bite; maculopapular or papulovesicular rash, sometimes on palms and soles
Rickettsia philipii rickettsiosis	5-14	Fever, headache, malaise, myalgia	Eschar or ulcerative lesion; lymphadenitis or lymphadenopathy
Mediterranean spotted fever (boutonneuse fever)	5-7	Fever, headache, muscle pain	Eschar (usually single)
Anaplasmosis	5-14	Fever, chills, rigors, severe headache, malaise, myalgia, gastrointestinal symptoms	Rare (<10%)
Human monocytic ehrlichiosis	5-14	Fever, chills, headache, malaise, muscle pain, gastrointestinal symptoms, altered mental status	Erythematous, maculopapular or petechial rash in <30% of adults and ~60% of children
Ehrlichia ewingii and *Ehrlichia muris eauclairensis* ehrlichioses	5-14	Fever, chills, headache, malaise, muscle pain, gastrointestinal symptoms, altered mental status	Rare

Of the other SFR infections, the first case of human *R parkeri* infection was documented in 2014; as of 2015, at least 40 cases have been identified.[33] It is carried by the Gulf Coast tick *(Amblyomma maculatum)*, and its geographic distribution extends from the Southern and Mid-Atlantic regions. Human infection with *R philipii* was first documented in 2010. *R philipii* is transmitted by the Pacific Coast tick (*Dermacentor occidentalis*), which is present in California and Oregon. Since 2010, 14 cases have been reported from California.[34]

SFR infection can also occur following international travel. Mediterranean spotted fever, also known as boutonneuse fever, has been reported in US patients following travel to Europe (Mediterranean basin), Middle East, Indian subcontinent, and Africa.[2] It is caused by *Rickettsia conorii* and transmitted from several species of *Ixodes* ticks.[35]

Anaplasmosis

Anaplasmosis (HGA) is caused by infection with *Anaplasma phagocytophilum*. The incidence rate is 7.3 cases per million person-years in the United States, and highest along the coastal Northeast and upper Midwest.[36] Anaplasmosis has substantial overlap of features with early Lyme disease but tends to be a more severe illness.[37] Infection is most common in adults 60 years and older; the case fatality rate (0.3%) is highest in adults 70 years and older, and those with compromised immune systems.[38]

The ticks that carry *A phagocytophilum* can also harbor *B burgdorferi, B miyamotoi* or *B microti*, and detection of coinfection is recommended as it may affect treatment choices.[5]

Ehrlichiosis

Ehrlichiosis can be caused by 3 bacteria in the United States: *Ehrlichia chaffeensis* (the cause of human monocytic ehrlichiosis), *Ehrlichia ewingii*, and *Ehrlichia muris eauclairensis*.[5] *E chaffeensis* is the most common cause of ehrlichiosis, and along with *E ewingii*, is most identified in South-Central, Southeastern, and Mid-Atlantic states.[39]

Ehrlichiosis that is caused by *E muris eauclairensis,* which shares the same tick vector (*I scapularis*) that spreads Lyme disease, has been reported in patients in Minnesota and Wisconsin.[39]

In recent decades, cases of ehrlichiosis have increased 10-fold, from 200 reported cases in 2000 to 2,093 cases in 2019.[39,40] The case fatality rate is highest for children younger than 5 years old (4%); however, the overall case fatality rate is about 1%.[39,41] Of the 218 cases of *E ewingii* ehrlichiosis reported to the CDC from 2008 to 2018, none were fatal.[39]

Tick-borne Non-Rickettsial Diseases

Babesiosis

Babesiosis is primarily caused by a protozoan parasite infection *(Babesia microti)*. This organism infects erythrocytes, and the disease process shares clinical features with malaria. Babesiosis is now reportable in 40 states but is most common in 7 states, which account for 86% of cases nationwide: Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, and Wisconsin.[42] Infection is primarily transmitted by ticks, although it can also be transmitted congenitally or through transfusion; 2 transfusion-associated cases were reported in 2018.[42] The disease may be asymptomatic, or symptoms may appear 1 to 6 weeks after the tick bite **(Table 3)**.[2] Symptoms vary widely but may include a gradual onset of irregular fever, chills, sweating, myalgia, arthralgia, nausea/vomiting, and fatigue **(Table 3)**.[2] Mild hepatosplenomegaly and mild hemolytic anemia may develop.[2] Treatment is not usually required for people without symptoms.[43]

Tularemia

Tularemia has been reported from nearly all US states but is most commonly found in parts of Massachusetts (including Martha's Vineyard, the site of two major outbreaks) and South Central and Pacific Northwest states. It is caused by the bacterium *Francisella tularensis* and transmitted through varying portals of entry including tick bites, skin contact with infected animals, and inhalation of contaminated aerosols or agricultural dust. Infection via tick bites is characterized by an ulcerative lesion at the site of the tick bite and by lymphadenopathy. An erythematous, tender, or pruritic papule typically appears within 3 to 5 days and subsequently enlarges to form an ulcer with a black base. Additional symptoms of tularemia appear abruptly and include fever, chills, headache, malaise, and fatigue **(Table 3)**.[2] Clinical consequences depend on the portal of entry and the extent of systemic involvement. Ulceroglandular tularemia is the most common form of tularemia and usually occurs following a tick or deer fly bite, or after handling of an infected animal. Less common forms include glandular, oropharyngeal, oculoglandular, and typhoidal tularemia. Pneumonic tularemia, a pulmonary form that may be contracted by inhalation, is the most serious form of tularemia and may spread through the bloodstream to the lungs if left untreated. Presumptive diagnosis is based on a history of exposure to a tick-endemic region and clinical signs and symptoms.

Table 3. Clinical Features of Tick-borne Non-Rickettsial Diseases[2]

Disease	Incubation period, days	Common signs and symptoms
Lyme disease	5-14	Fever, chills, headache, myalgia, arthralgia, lymphadenitis or lymphadenopathy, rash
Babesiosis	7-63	Fever, chills, sweats, malaise, fatigue, myalgia, arthralgia, headache, gastrointestinal symptoms, dark urine
Tularemia	3-5[a]	Fever, chills, headache, malaise, fatigue, anorexia, myalgia, chest discomfort, cough, sore throat, vomiting, diarrhea, abdominal pain
Powassan virus neuroinvasive disease/ encephalitis	7-28	Fever, headache, vomiting, weakness, neurological symptoms including altered mental status, seizures, movement disorders
Colorado tick fever	1-14	Fever, chills, headache, myalgia, lethargy
Borrelia miyamotoi disease	Days to weeks[b]	Fever, chills, fatigue, severe headache, arthalgia/myalgia, dizziness, confusion
Heartland and Bourbon virus diseases	Unknown[b]	Fever, fatigue, decreased appetite, headache, arthralgia, myalgia, nausea, diarrhea
Tick-borne relapsing fever	~7	Headache, myalgia, chills, nausea, vomiting, arthralgia, rash

[a]Incubation period may range 1-21 days.
[b]Specific ranges are unknown.

Colorado Tick Fever

Colorado tick fever (CTF) is caused by an arbovirus (Colorado tick fever virus) that infects erythrocytes. It is found throughout the Rocky Mountain region of the United States. Although CTF is not a nationally notifiable condition, a total of 59 cases of CTF were reported to the CDC from 2010 through 2019. After a mean incubation time of 1 to 14 days, common presenting symptoms include fever, chills, headache, body aches, lethargy, and a characteristic biphasic pattern of fever termed "saddleback" fever. The fever lasts for 2 to 3 days, disappears, and then may recur for another 2 to 3 days. In rare instances, severe complications such as central nervous system involvement and hemorrhage may occur, especially in children. Specific antiviral treatment is not available for CTF.[44]

Borrelia miyamotoi Disease

B miyamotoi has been detected in both *Ixodes* species ticks (*I scapularis and I pacificus*) that transmit *B burdorferi*, indicating that BMD may share the same geographic distribution as Lyme disease.[45] The clinical presentation of BMD is variable but shares a similar spectrum with other tick-borne diseases such as Lyme disease, anaplasmosis, and babesiosis.[46] A constellation of nonspecific symptoms commonly includes fever, severe headache, myalgia, fatigue, and arthralgia; symptoms are characteristic of Lyme disease, babesiosis, and anaplasmosis which may be included in a differential diagnosis.[46] A "toxic" appearance suggestive of sepsis is common on presentation and is often accompanied by elevated liver enzyme levels, neutropenia, and thrombocytopenia in patients hospitalized for suspected infection.[47]

Tick-borne Relapsing Fever

Tick-borne relapsing fever (TBRF) is caused by *Borrelia hermsii* and occurs west of the Mississippi River, especially in forested mountainous areas of the far Western states. Transmission typically occurs while sleeping in cabins or other rustic buildings that may house ticks in animal nests concealed in walls, attics, or crawl spaces. TBRF is characterized by recurrent acute episodes of spirochetemia and fever. Following a mean incubation period of 7 days, the onset of illness is sudden, with headache, myalgia, chills, nausea/vomiting, and arthralgias that may be severe **(Table 3)**.[2] Fever is typically ≥104°F and may be accompanied by delirium. Leukocytosis and thrombocytopenia are common, and splenomegaly may be present. Microscopy can be utilized to visualize the spirochetes in a blood smear, and thus, is useful in establishing the diagnosis.

Symptoms intensify without treatment; therefore, treatment should be administered when clinical suspicion is high.

INDIVIDUALS SUITABLE FOR TESTING

- Symptomatic individuals with a history of exposure to a tick-endemic area

TEST AVAILABILITY

Laboratory tests that can help confirm the clinical diagnosis include tick identification, microscopic visualization of the causative organism in blood or other clinical specimens, various serologic techniques, culture, and polymerase chain reaction (PCR)-based assays **(Table 4)**. Panel components may be ordered individually.

TEST SELECTION AND INTERPRETATION

In most cases, presumptive diagnosis of tick-borne illnesses is based on clinical grounds. Treatment should not be delayed pending confirmatory laboratory results except in the prophylaxis of Lyme disease in persons bitten by *I scapularis* or *I pacificus* ticks where empiric treatment is not recommended. The clinical symptoms and type of rash or lesion, if present, guide the initial differential diagnosis among patients exposed to a tick-endemic area **(Figure)**.[48] This, in turn, guides appropriate test selection, presumably leading to confirmation of the suspected disorder. The sections below outline characteristic test results for each of the tick-borne diseases discussed.

LYME DISEASE

A timeline of tick exposure in a tick-endemic area and symptoms of Lyme disease guide appropriate test selection.[11,16,30] The CDC recommends testing for IgM or IgG antibodies using either standard 2-tiered testing (STTT) or modified 2-tiered testing (MTTT).[49,50] MTTT detects up to 30% more cases compared to STTT in patients with early Lyme disease.[51,52] PCR is recommended for some non-Lyme, tick-borne diseases (eg, BMD, Powassan virus infection, and anaplasmosis) that are included in Lyme disease differential diagnosis.[12,24,27,53-55] 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.[11,56] The IDSA suggests that PCR methodology not be used for the diagnosis of Lyme disease.[30] However, in patients at less than 2 weeks after symptom onset, PCR may be helpful to identify non-Lyme tick-borne diseases if there is diagnostic uncertainty or if mixed infection is suspected.[12,23,24,27,53-55] Two-tiered tests should be used 2 to 4 weeks following a tick bite; an increase in IgM titers may not be detected in specimens collected within 2 weeks following a tick bite.[11,57]

IgM antibodies may be present within a few weeks of disease onset, whereas large increases in IgG titers are produced months later; thus, 2-tiered testing that is positive for IgM and negative for IgG indicates early infection.

Early disseminated Lyme disease

Two-tiered testing is recommended when clinical findings are suggestive of early disseminated Lyme disease **(Table 5)**. 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. 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. A positive IgG result by 2-tiered testing is required to confirm the diagnosis of early disseminated Lyme disease, but does not differentiate between active and past *B burgdorferi* infection.[23,58]

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. PCR-based assays 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%).[59] Untreated patients who continue to be symptomatic but are seronegative for 6 to 8 weeks are unlikely to have Lyme disease, and a differential diagnosis should be considered.[30]

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 Lyme neuroborreliosis 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%).[29,59] A diagnosis of Lyme neuroborreliosis can be supported if *Borrelia* antibody or DNA are detected in cerebrospinal fluid (CSF). Antibody levels in CSF can be measured by ELISA or nephelometry and compared to control levels (ie, serum antibody or albumin) in a ratio defined as an antibody index; an elevated antibody index strongly supports a diagnosis of Lyme neuroborreliosis.[60] *Borrelia* DNA in CSF can be detected by PCR-based assays, which can support a diagnosis of Lyme neuroborreliosis; however, detection by PCR may be limited owing to low clinical sensitivity (38%).[61]

TICK-BORNE RICKETTSIAL DISEASES

Diagnosis of TBRDs is primarily clinical. However, laboratory testing can play an important role in distinguishing among these closely related diseases and in confirming infection.

Anaplasmosis and ehrlichiosis infections are characterized by infection of leukocytes, in which the causative agents multiply in cytoplasmic membrane-bound vacuoles called morulae.[62] *A phagocytophilum* and *E ewingii* infect granulocytes, whereas *E chaffeensis* infects monocytes. Thus, visualization of morulae on a routine blood smear may provide the first clue for diagnosis and help differentiate HME from HGA and

Table 4. Tests Available for Diagnosis and Management of Tick-borne Diseases

Test code	Assay	Method	Clinical use
All Tick-borne Diseases			
94322	Tick-borne Disease, Acute Molecular Panel[a,b] Includes *Anaplasma phagocytophilum* DNA, Qualitative Real-Time PCR; *Babesia microti* DNA, Real-Time PCR; *Borrelia miyamotoi* DNA, Real-Time PCR, Miscellaneous; *Ehrlichia chaffeensis* DNA, Real-Time PCR; Lyme Disease *(Borrelia spp)* DNA, Qualitative, Real-Time PCR, Blood	Real-time PCR	Diagnose tick-borne diseases when selecting tests for individual pathogen is challenging due to overlapping geographic distributions and clinical presentations of illness; especially useful to diagnose mixed infections
36942	Tick-borne Disease, Antibody Panel[a,b] Includes *Anaplasma phagocytophilum* Antibodies (IgG and IgM)[a]; *Babesia duncani* (WA1) IgG Antibody, IFA[a]; *Babesia microti* Antibodies (IgG, IgM); Lyme Disease Ab with Reflex to Blot (IgG, IgM); *Ehrlichia chaffeensis* (IgG, IgM)	IFA	Diagnose tick-borne diseases when selecting tests for individual pathogens is challenging owing to substantial clinical overlap and coinfection

(Continued)

Table 4. Tests Available for Diagnosis and Management of Tick-borne Diseases *(Continued)*

Test Code	Assay	Method	Clinical use
3946(X)	Tick (and Other Arthropods) Identification	Microscopy	Identify tick to determine risk of tick-borne disease; assist with differential diagnosis
Lyme disease			
39209	*Borrelia burgdorferi* DNA, Qualitative Real-Time PCR, Miscellaneous[b,c]	Real-time PCR	Diagnose Lyme disease
39219	*Borrelia* Species DNA, Real-Time PCR, with Reflexes, Blood[b,c,d]	Real-time PCR	Detect *Borrelia* spp DNA; diagnose Lyme disease or *B miyamotoi* disease
39218	*Borrelia* Species DNA, Real-Time PCR, with Reflexes, Synovial Fluid/CSF[b,c,d]	Real-time PCR	Detect *Borrelia* spp DNA; diagnose Lyme disease or *B miyamotoi* disease
6646	Lyme Disease (*Borrelia* spp) Antibody 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)[d]	Immunoassay	Diagnose Lyme disease by modified 2-tiered test
34194	Lyme Disease Antibody Index for CNS Infection Includes *Borrelia burgdorferi* IgG, IgM Antibodies (CSF and Serum); Total IgG and Total IgM (CSF and Serum); Albumin (CSF and Serum); *Borrelia burgdorferi* Antibody Index; Albumin Ratio	ELISA; Nephelometry	Diagnose Lyme neuroborreliosis
29477	Lyme Disease Antibody (IgG), Immunoblot	Immunoblot	Diagnose Lyme disease when ELISA results are positive or equivocal
8593	Lyme Disease Antibodies (IgG, IgM), Immunoblot		
15777	Lyme Disease (*Borrelia* spp) DNA, Qualitative Real-Time PCR, Blood[b]	Real-time PCR	Detect *Borrelia* spp DNA
15564	Lyme Disease (*Borrelia* spp) DNA, Qualitative Real-Time PCR, CSF/Synovial Fluid[b]	Real-time PCR	Diagnose Lyme neuroborreliosis or Lyme arthritis
15510	Lyme Disease (*Borrelia* spp) DNA, Qualitative, Real-Time PCR, Tick[b]	Real-time PCR	Detect *B burgdorferi* in tick to assess risk of Lyme disease
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
Spotted fever rickettsiosis			
15332	*Rickettsia conorii* Antibody Panel, IFA[b]	IFA	Diagnose *Rickettsia conorii* infection
70191	*Rickettsia rickettsii* DNA, Real-Time PCR[b]	Real-time PCR	Diagnose RMSF
6419	*Rickettsia* (RMSF) Antibodies (IgG, IgM) with Reflex to Titers[d]	IFA	

(Continued)

Table 4. Tests Available for Diagnosis and Management of Tick-borne Diseases *(Continued)*

Test Code	Assay	Method	Clinical use
37507	*Rickettsia* Antibody Panel with Reflex to Titers[d] Includes IgG and IgM to causative organisms of RMSF and typhus fever	IFA	Differential diagnosis of rickettsial disease
37478	Rickettsial Disease Panel[a] Includes IgG and IgM to causative organisms of RMSF, typhus fever, with reflex to appropriate titers	IFA	
37503	*Rickettsia* (Typhus Fever) Antibodies (IgG, IgM) with Reflex to Titers[d]	IFA	
Anaplasmosis			
34464(X)	*Anaplasma phagocytophilum* Antibodies (IgG, IgM)[b]	IFA	Diagnose HGA
17320	*Anaplasma phagocytophilum* DNA, Qualitative, Real-Time PCR[b]	Real-time PCR	
10611(X)	*Anaplasma phagocytophilum* and *Ehrlichia chaffeensis* Antibody Panel[a] Includes IgG and IgM for both organisms	IFA	Differential diagnosis of ehrlichiosis
Ehrlichiosis			
34271(X)	*Ehrlichia chaffeensis* Antibodies (IgG, IgM)[b]	IFA	Diagnose HME
11353	*Ehrlichia chaffeensis* DNA, Real-Time PCR[b]	Real-time PCR	
70194(X)	*Ehrlichia ewingii* DNA, Real-Time PCR[b,e]	Real-time PCR	
Babesiosis			
34300	*Babesia microti* Antibodies (IgG, IgM)[b]	IFA	Diagnose babesiosis
37314	*Babesia microti* DNA, Real-Time PCR[b]	Real-time PCR	
17231	*Babesia duncani* (WA1) Antibody (IgG), IFA[b]	IFA	
831	Malaria/Babesia/Other Blood Parasites	Microscopy	
Tularemia			
91122	Febrile Antibodies and *Francisella* Panel[a,b,d] Includes IgG and IgM to causative organisms of RMSF and typhus, with reflex to appropriate titers; total antibody to Salmonella (Salmonella H types A, B, D; Salmonella O types D, Vi); IgG and IgM to *Brucella*, with reflex to agglutination; and antibody to *Francisella tularensis*	See individual tests	Differential diagnosis of febrile disease
91121	Febrile Antibodies Panel[a,b,d] Includes IgG and IgM to causative organisms of RMSF and typhus, with reflex to appropriate titers; total antibody to *Salmonella* (*Salmonella* H types A, B, D; *Salmonella* O types D, Vi); IgG and IgM to *Brucella*, with reflex to agglutination		
35176(X)	*Francisella tularensis* Antibody, DA[b]	Direct Agglutination	Diagnose tularemia

(Continued)

Table 4. Tests Available for Diagnosis and Management of Tick-borne Diseases *(Continued)*

Test Code	Assay	Method	Clinical use
10443	*Francisella tularensis* Screen[c]	Culture	Screen for tularemia
***Borrelia miyamotoi* disease**			
39684	*Borrelia miyamotoi* Antibodies (IgG, IgM), Immunoassay	Immunoassay	Diagnose *B miyamatoi* infection
93795	*Borrelia miyamotoi* DNA, Real-Time PCR, Miscellaneous[b]	Real-time PCR	Confirm diagnosis of *B miyamotoi* infection
93794	*Borrelia miyamotoi* DNA, Real-Time PCR, Tick[b]	Real-time PCR	Detect *B miyamotoi* in tick to assess risk of human infection
39219	*Borrelia* Species DNA, Real-Time PCR, with Reflexes, Blood[b,c,d]	Real-time PCR	Detect *Borrelia* spp DNA; diagnose Lyme disease or *B miyamotoi* disease
39218	*Borrelia* Species DNA, Real-Time PCR, with Reflexes, Synovial Fluid/CSF[b,c,d]	Real-time PCR	Detect *Borrelia* spp DNA; diagnose Lyme disease or *B miyamotoi* disease
Colorado Tick Fever			
34986	Colorado Tick Fever Antibodies (IgG, IgM)[b]	IFA	Diagnose Colorado tick fever

EIA, enzyme immunoassays; ELISA, enzyme-linked immunosorbent assay; HGA, human granulocytic anaplasmosis, formerly known as human granulocytic ehrlichiosis (HGE); HME, human monocytic ehrlichiosis; IFA, immunofluorescence assay; PCR, polymerase chain reaction; TBRF, tick-borne relapsing fever.

[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).

[e] Available from Quest Diagnostics Nichols Institute.

E ewingii infection. Positive results may be seen in up to 60% of patients with HGA and to a lesser extent in patients with HME.[5]

Routine laboratory tests are also useful in assessing patients suspected of having tick-borne illness and can provide supportive evidence of specific illnesses; test results associated with the TBRDs are listed in Table 6.[5,63] For example, patients with HGA often present with slightly decreased platelet and WBC counts and elevated liver enzymes. Although such abnormalities are suggestive of HGA, these markers tend to stabilize over time. Therefore, normal levels do not rule out HGA, especially in patients who have had symptoms for more than 1 week.[64] Patients with early RMSF often have normal or slightly altered laboratory values. Band neutrophil counts may be increased; because such band increases are uncommon in viral infections, they can help in differential diagnosis. Markers of tissue injury may arise later during the disease course.

Laboratory testing may confirm the presumptive clinical diagnosis and is important from an epidemiology and public health perspective. Confirmatory laboratory testing for TBRDs includes serology and nucleic acid testing **(Table 6)**.[5] IFAs are considered the gold standard for TBRD serology testing.[5] A 4-fold rise in titer of IgG or IgM in paired acute and convalescent samples collected 2 to 3 weeks apart is essential to confirm acute infection. For RMSF, IgG and IgM increase concurrently; IgM wanes after 3 to 4 months, whereas IgG persists for 7 to 8 months.

Note: although most patients have positive IgG or IgM antibody by the second week of illness, many people will be seronegative at the time of the first test (especially if done within the first week or so of illness). Therefore, negative results on serologic tests should not lead to discontinuation of therapy.[5]

Detection of DNA in whole blood is especially useful for confirming HGA, HME, and *E ewingii* infection because these organisms infect circulating leukocytes. For RMSF, detection of *R rickettsii* in blood is more likely in advanced disease or fulminant infection. Positive results confirm TBRD, but negative results do not exclude the diagnosis.

TICK-BORNE NON-RICKETTSIAL DISEASES

Babesiosis

The current case definition for babesiosis requires the presence of clinical evidence (fever, anemia, or thrombocytopenia) and/or at least 1 subjective symptom (chills, sweats, headache, myalgia, or arthralgia).[65] Laboratory confirmation of infection may include microscopic identification or nucleic acid amplification detection of *Babesia species* DNA **(Table 7)**.[2] Serologic studies may provide supportive laboratory evidence **(Table 7)**.[2]

Laboratory test results, combined with clinical symptoms, are used to make treatment decisions.[2,11] Treatment is recommended in symptomatic patients when babesial parasites have been identified in peripheral blood smears or when DNA results are positive. Treatment is not recommended in symptomatic patients whose blood is negative for babesial parasites or DNA, even if serology testing is positive. Also, treatment is not recommended for asymptomatic individuals, regardless of laboratory test results. Asymptomatic individuals with positive babesial smears and/or DNA results should have these tests repeated, and treatment should be considered if repeat testing is positive >3 months later.

Tularemia

Various methods are available to assist in the diagnosis of tularemia. Positive results for *F tularensis* using direct agglutination assay provides presumptive evidence. Culture of *F tularensis* from appropriate sites provides definitive evidence of tularemia but requires biosafety level 3 precautions. Francisella tularensis serology testing is the primary laboratory approach to confirm a diagnosis of tularemia **(Table 7)**.[2,66] A 4-fold increase in antibody titer between acute and convalescent sera (collected at least 4 weeks after onset) is considered diagnostic.[2,66]

Colorado Tick Fever

Leukopenia is characteristically seen in a CBC, and thrombocytopenia may be present. Acute and convalescent

Table 5. Lyme Disease: Clinical Features and Recommended Laboratory Testing[11,12,20-25]

Stage of disease	Symptom onset	Symptoms	Laboratory testing
Early localized	3-30 days after tick bite	• EM • Fever, myalgia, headache, nausea, fatigue	<2 weeks after the onset of symptoms: skin lesions that are atypical for EM or a mixed infection (eg, Lyme disease and *B miyamotoi* disease) is clinically suspected, tick-borne PCR panel may be useful in the diagnosis of tick-borne disease 2-4 weeks after the onset of symptoms: acute (symptomatic) and convalescent (recovered) 2-tiered[a] IgG, IgM serology (if skin lesions that are atypical for EM)
Early disseminated	2 weeks to months after tick bite	• Atrioventricular heart block sometimes with myopericarditis • Migratory pain in joints, bone, and muscle • Secondary annular lesions • Malaise, fatigue	2-4 weeks after the onset of symptoms: acute and/or convalescent 2-tiered[a] IgG, IgM serology >4 weeks after the onset of symptoms: acute and/or convalescent 2-tiered[a] IgG serology
Late-stage	Months to years after tick bite	• Encephalopathy, polyneuropathy, lymphocytic meningitis • Prolonged, chronic arthritis • Lymphocytoma • Fatigue	Acute and/or convalescent 2-tiered[a] IgG serology in serum; consider serology and/or detection of *B burgdorferi* DNA in CSF or synovial fluid

CSF, cerebrospinal fluid; EM, erythema migrans; PCR, polymerase chain reaction.
[a] Two-tiered testing is a follow-up of a positive or equivocal ELISA with an immunoblot test (standard 2-tiered test) or a second ELISA (modified 2-tiered test), as recommended by the Centers for Disease Control and Prevention and the Association of State and Territorial Public Health Laboratory Directors.[49,50]

Table 6. Laboratory Confirmation of Tick-borne Rickettsial Diseases[5,63]

Disease	Common laboratory abnormalities	Confirmatory laboratory tests	Laboratory criteria for confirmation of diagnosis
Rocky Mountain spotted fever (*Rickettsia rickettsii*)	• WBC count normal or slight ↑ • Immature neutrophils ↑ • Platelet count ↓ • Sodium ↓ • Transaminases slight ↑	Acute and convalescent serology *or*	4-fold increase in antibody titer
		R rickettsii DNA	Detected
Rickettsia parkeri rickettsiosis	• WBC count ↓ • Platelet count slight ↓ • Transaminases slight ↑	Acute and convalescent serology *or*	4-fold increase in antibody titer
		Rickettsia philipii DNA	Detected
Rickettsia philippi rickettsiosis	• Not documented	Acute and convalescent serology *or*	4-fold increase in antibody titer
		R parkeri DNA	Detected
Mediterranean spotted fever (boutonneuse fever)	• WBC count ↓ • Immature neutrophils ↑ • Platelet count ↓ • Sodium ↓ • Transaminases ↑	Acute and convalescent serology	4-fold increase in antibody titer
Human granulocytic anaplasmosis	• WBC count slight ↓ • Platelet count slight ↓ • Transaminases ↑	Acute and convalescent serology *or*	4-fold increase in antibody titer
		A phagocytophilum DNA *or*	Detected
		Identification of morulae in WBCs and serology	Morulae detected and positive antibody titer
Human monocytic ehrlichiosis	• WBC count ↓ in ≤53% • Platelet count ↓ in ≤94% • Transaminases ↑ (2-8 times ULN) • Sodium ↓ • Anemia	Acute and convalescent serology *or*	4-fold increase in antibody titer
		E chaffeensis DNA *or*	Detected
		Identification of morulae in WBCs and serology	Morulae detected and positive antibody titer
Ehrlichia ewingii ehrlichiosis	• WBC count ↓ • Platelet count ↓ • Transaminases ↑	Acute and convalescent serology *or*	4-fold increase in antibody titer
		E ewingii DNA	Detected
Ehrlichia muris-like (EML) agent ehrlichiosis	• WBC count ↓ • Platelet count ↓ • Lymphocytes ↓ • Transaminases ↑ • Anemia	Acute and convalescent serology *or*	4-fold increase in antibody titer
		EML DNA	Detected

↑, increased; ↓, decreased; ULN, upper limit of normal.

serology should be considered for patients with clinically suspected CTF **(Table 7)**.[2,67] A 4-fold rise of IgG or IgM titer in paired acute and convalescent samples confirms the diagnosis; the detection of IgM indicates acute infection.[2]

Borrelia miyamotoi Disease

PCR amplification of *B miyamotoi* DNA is part of an acute molecular panel of tests used to confirm a presumptive diagnosis of BMD based on clinical presentation. CSF, synovial fluid, whole blood or urine are acceptable specimen types for analysis. Detection of *B miyamotoi* DNA in suspected tick specimens is supportive for the diagnosis of infection.[2] Guidelines also indicate serologic testing to confirm the diagnosis of BMD.[2] Positive results on serology by ELISA or IgM and IgG immunoblot, however, may indicate coinfection by *Borrelia* species such as *B burgdorferi* and/or *B hermsii*.[2] Negative results do not rule out infection and may be due to testing prior to seroconversion during the acute phase of infection.[68]

Tick-borne Relapsing Fever

Diagnosis of TBRF is made by the detection of spirochetes in the patient's blood during periods of high fever (sensitivity ~70%). The diagnosis is confirmed by serology testing.[2] The presence of *B hermsii* IgM titers ≥1:16 are associated with acute infection, while IgG titers ≥1:64 reflect later stages of disease. Single IgG titers ≥1:64 are considered presumptive evidence of infection and a 4-fold increase in titer between acute and convalescent sera provides evidence of recent or current infection **(Table 7)**.[69] Because other *Borrelia* and *Treponema* species cross-react in the IFA test, positive specimens should be tested for antibodies to these organisms.

Table 7. Laboratory Confirmation of Tick-borne Non-Rickettsial Diseases[2]

Disease	Common laboratory abnormalities	Confirmatory laboratory tests	Laboratory criteria for confirmation of diagnosis
Babesiosis[a]	• Hematocrit ↓ • Creatinine, BUN ↑ • Platelet count ↓ • Transaminases ↑ (±)	Light microscopy of stained blood smears *or*	Identification of *Babesia* organisms in RBCs
		Nucleic acid amplification of *Babesia* DNA *or*	Detected
		Isolation of *Babesia* organisms by animal inoculation from whole blood	Isolated
Tularemia	• WBC count ↑ (±) • Platelet count ↓ (±) • Transaminases ↑ (±) • CPK ↑ (±)	Acute and convalescent serology	4-fold increase in antibody titer
Colorado tick fever	• WBC count ↓ • Platelet count ↓ (±)	Acute and convalescent serology	4-fold increase in antibody titer; positive IgM antibody titer
Borrelia miyamotoi disease	• WBC count ↓ • Transaminases ↑ • Platelet count ↓	*B miyamotoi* DNA (PCR)	Detected
Tick-borne relapsing fever	• Platelet count ↓	Acute and convalescent serology	4-fold increase in antibody titer

BUN, blood urea nitrogen; CPK, creatine phosphokinase; IFA, immunofluorescence assay; IHC, immunohistochemistry; PCR, polymerase chain reaction; ULN, upper limit of normal; ↑, increased; ↓, decreased; ±, may be present.

[a] Demonstration of at least 1 of the following provides supportive but not confirmatory laboratory evidence of babesiosis: *B microti* total Ig or IgG antibody titer ≥1:256 by IFA (≥1:64 for epidemiologically-linked blood donors or recipients); *B microti* IgG by immunoblot; *B divergens* total Ig or IgG titer ≥1:256 by IFA; or *B duncani* total Ig or IgG ≥1:512 by IFA.[65]

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