

LEARNING OBJECTIVE: Readers will consider tickborne illnesses in patients with known or potential tick exposure presenting with fever or vague constitutional symptoms in tick-endemic regions

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Tickborne diseases other than Lyme in the United States

ABSTRACT

Tickborne diseases are increasing in the United States, and the geographic range of tick vectors is expanding. Tickborne diseases are challenging to diagnose, as they present with vague symptoms such as fever, constitutional symptoms, and nonspecific laboratory abnormalities. A high degree of clinical suspicion is required to make a diagnosis, as patients often do not recall a tick bite. The availability of laboratory testing for tickborne diseases is limited, especially in the acute setting. Therefore, if a tickborne disease is suspected, empiric therapy should often be initiated before laboratory confirmation of the disease is available. This article summarizes the most common non-Lyme tickborne diseases in the United States.

KEY POINTS

Tickborne illnesses should be considered in patients with known or potential tick exposure presenting with fever or vague constitutional symptoms in tick-endemic regions.

Given that tick-bite history is commonly unknown, absence of a known tick bite does not exclude the diagnosis of a tick-borne illness.

Starting empiric treatment is usually warranted before the diagnosis of tickborne illness is confirmed.

Tick avoidance is the most effective measure for preventing tickborne infections.

TICKS ARE RESPONSIBLE for most vector-borne infections in the United States. Most infections occur between April and October, when tick populations peak.¹ However, infections can occur year-round.^{2,3}

Tick bites are often unnoticed because the ticks are small when they are at the infective stage of their life cycle, and their attachment is characteristically painless and often in intertriginous body sites.¹ Therefore, absence of a known tick bite never precludes the diagnosis of a tickborne infection.^{1,4,5}

Although rural outdoor activities are recognized risk factors, tickborne infections also occur in urban areas.⁶ Thus, the lack of classic epidemiologic clues does not rule out a diagnosis of tickborne infection.

In most cases, tickborne illnesses present with nonspecific symptoms such as fever, malaise, headache, nausea, and myalgia. Accurate diagnosis of tickborne diseases can be challenging due to the similar clinical manifestations and overlapping geographic distributions of potential tick vectors.¹

This review summarizes the epidemiology, clinical features, treatment, and prevention of the most prevalent non-Lyme tickborne diseases of the United States: Rocky Mountain spotted fever (RMSF), other spotted fever group rickettsial (SFGR) infections, ehrlichiosis, babesiosis, tickborne relapsing fever, *Borrelia miyamotoi* infection, southern tick-associated rash illness (STARI), tularemia, and tickborne viral infections.

■ ROCKY MOUNTAIN SPOTTED FEVER

RMSF (Table 1) is caused by *Rickettsia rickettsii*, an obligate intracellular gram-negative coccobacillus.^{7,8}

TABLE 1

Rocky Mountain spotted fever**Pathogen:** *Rickettsia rickettsii***Tick vectors:** *Dermacentor variabilis*, *Dermacentor andersoni*, *Rhipicephalus sanguineus***Geographic distribution:** Widespread; most common in south-central and south-Atlantic regions**Classic presentation:** Fever, headache, rash, weakness, malaise, myalgia, thrombocytopenia, anemia, hyponatremia, increased aminotransferase levels**Diagnosis:** Serologic antibody testing with a 4-fold increase between acute and convalescent serology with a minimum peak titer $\geq 1:64$; polymerase chain reaction assay with low sensitivity; immunohistochemistry and cell culture rarely used**Treatment:** Doxycycline, typically for 7 days (range 5–10 days)

**Absence
of a known
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Dermacentor variabilis, the American dog tick, is the major vector in the southern and eastern United States, and *D andersoni*, the Rocky Mountain wood tick, is the most common vector in the western United States.^{4,7,8} *Rhipicephalus sanguineus*, the brown dog tick, has also been found to transmit RMSF in Arizona.^{9,10}

While most infections in humans are transmitted by tick bite, rare cases of RMSF are contracted through exposure to infective tick hemolymph during tick removal, parenteral inoculation or infectious aerosols in laboratory settings, and blood transfusion.^{7,8}

The geographic distribution of RMSF is restricted to the Western Hemisphere. Within the United States, cases of RMSF have been reported in nearly every state.⁴ However, RMSF is most prevalent in North Carolina, Tennessee, Missouri, Arkansas, and Oklahoma (Figure 1).¹

RMSF is both the most common and the most likely cause of death among rickettsial infections in the United States.^{4,7,8} Most cases occur in children ages 5 to 9.^{10,11} The case-fatality rate is over 20% without antimicrobial therapy but less than 1% with timely and appropriate antibiotic treatment.^{7,8}

Clinical manifestations of Rocky Mountain spotted fever

RMSF is transmitted after only 2 to 20 hours of tick attachment, and symptoms begin 3 to 12 days after inoculation.^{1,7,8} Unlike many other species that cause SFGR infection, *R rickettsii* does not cause an eschar at the site of inoculation.^{7,12}

The classic triad of RMSF is fever, headache, and a rash. This triad is present in only 3% of early infections, but the prevalence increases to 60% to 70% by 2 weeks after the tick bite.^{1,7} Other common initial symptoms include generalized malaise, weakness, and myalgia.^{7,8,12} Gastrointestinal symptoms are common, and RMSF can be misdiagnosed as gastroenteritis, particularly in children.⁸

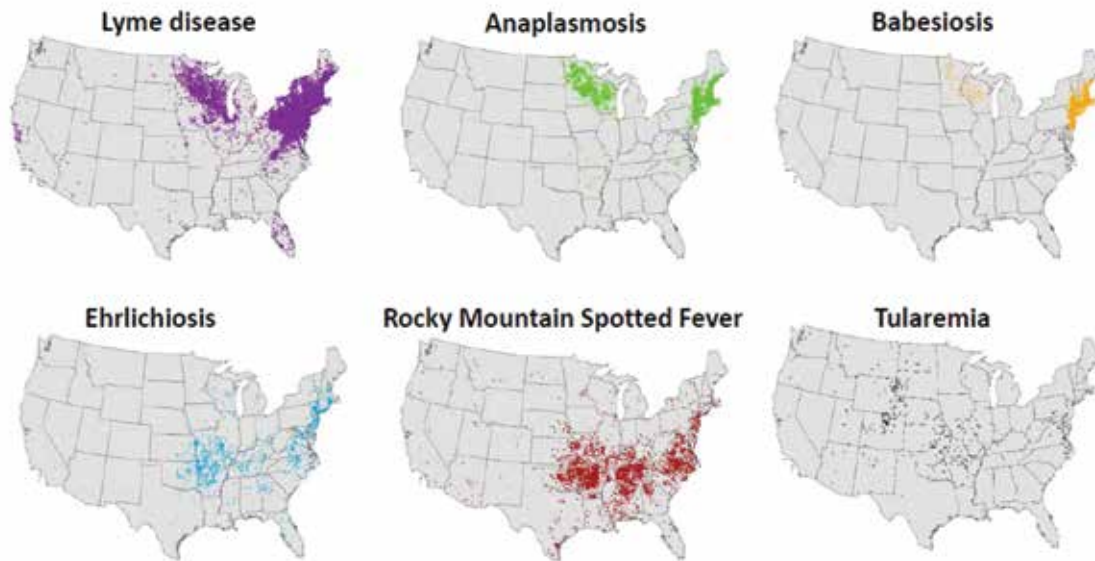
A rash usually occurs. It is due to systemic vasculitis and endothelial injury and often presents 2 to 5 days after the onset of fever, which can delay diagnosis.^{7,12,13} It usually progresses from macular to petechial and begins on the ankles, forearms, and wrists, spreading centripetally to the trunk and face and often including the palms and soles.⁷ Large areas of ecchymosis, ulceration, and (uncommonly) gangrene may occur as lesions coalesce.^{7,8} The 10% of patients who do not develop a rash (“spotless” fever) tend to have a poorer prognosis due to delayed diagnosis.⁸

Risk factors for severe disease include delay or lack of appropriate treatment, extremes of age, Native American descent, glucose-6-phosphate dehydrogenase deficiency, and immunocompromised states.^{1,10,11,13} Complications from the widespread *Rickettsia*-induced vasculitis may include a septic or toxic shock-like syndrome and neurovascular, cardiac, respiratory, and renal damage.^{7,11} Without appropriate therapy, death occurs 7 to 15 days after symptom onset.⁸

Laboratory evaluation may reveal thrombocytopenia and anemia.⁷ Leukocytosis or leukopenia may be present.⁸ Hyponatremia, elevated aminotransferase levels, elevated creatine kinase levels, prolonged coagulation times, and decreased fibrinogen may also be present.^{7,8}

Diagnosis of Rocky Mountain spotted fever

No diagnostic studies are available for the acute phase of RMSF. Therefore, a high suspicion of RMSF is essential, and treatment



Each dot represents a reported case in the county of residence

FIGURE 1. Geographic distribution of nationally notifiable tickborne diseases, 2015.

Eisen R. Emerging tickborne diseases. CDC Public Health Grand Rounds, March 21, 2017. www.cdc.gov/cdcgrandrounds/archives/2017/March2017.htm. Accessed June 7, 2017.

should be started as soon as RMSF is suspected. Confirmatory testing can retrospectively validate a clinical diagnosis.^{4,7,11}

Serologic testing with an immunofluorescence antibody assay remains the principal diagnostic test for RMSF, and paired testing (during the acute and convalescent phases) has a sensitivity of 94%.⁴ A 4-fold or greater increase in antibody titer (with a minimum titer of 1:64) between acute and convalescent samples is considered diagnostic of acute infection.^{4,7,8} Serology is often negative early in the disease course.^{4,7,8} The assay cross-reacts with other SFGR species, however.^{4,8}

Amplification of *R. rickettsii* DNA by polymerase chain reaction (PCR) from blood or biopsy sites can be done in some research settings, but its utility is limited because of low sensitivity early in the course of the infection.^{4,7}

Immunohistochemical staining of a skin biopsy or autopsy specimen is a highly specific diagnostic test performed at a limited number of laboratories, though it has a sensitivity of only 60% to 92%.^{4,7,8}

Cell culture can also be performed, but only in biosafety level 3 (scale of 1 to 4) laboratories.¹

Treatment of Rocky Mountain spotted fever

Prompt initiation of antibiotic therapy greatly improves prognosis.^{1,13,14}

Doxycycline for 7 days is the treatment of choice for RMSF, including in pregnant patients with life-threatening disease and in children.^{4,7,8,15,16}

Tetracycline can also be used.

Chloramphenicol is an alternative treatment for pregnant patients with mild to moderate disease or those patients with a severe hypersensitivity reaction to doxycycline.^{1,4,7,9,15,16} In the United States, chloramphenicol is currently available only in an intravenous formulation.

Fever typically subsides within 24 to 48 hours of starting treatment.^{4,8} Failure to clinically improve within 48 hours suggests an alternative diagnosis.^{1,4} Long-term complications of severe infection may include hearing loss, blindness, and amputation of digits or extremities due to gangrene.^{1,8} Persistence of disease beyond acute infection has not been observed.¹

OTHER SPOTTED FEVER GROUP RICKETTSIAL INFECTIONS

Two other SFGR infections, uncommon in the United States, are caused by *R. parkeri* (Ta-

The case-fatality rate of RMSF is > 20% without treatment, < 1% with treatment

TABLE 2

Rickettsia parkeri infection

Tick vector: *Amblyomma maculatum*

Geographic distribution: Eastern and southern regions

Classic presentation: Inoculation eschar, fever, headache, myalgia, rash, thrombocytopenia, leukopenia, increased aminotransferase levels

Diagnosis: Same as for Rocky Mountain spotted fever

Treatment: Same as for Rocky Mountain spotted fever

TABLE 3

Rickettsia species 364D infection

Tick vector: *Dermacentor occidentalis*

Geographic distribution: Northern California, Pacific coast

Classic presentation: Inoculation eschar, fever, headache, myalgia

Diagnosis: Same as for Rocky Mountain spotted fever

Treatment: Same as for Rocky Mountain spotted fever

ble 2) and *Rickettsia* species 364D (Table 3).

Both infections are characterized by an inoculation eschar. Symptoms include fever, headache, myalgia, and regional lymphadenopathy.¹ Rash (most often maculopapular or vesicopustular) is characteristic of *R parkeri*, but it is not common in *Rickettsia* species 364D rickettsiosis.^{17,18} Mild thrombocytopenia, leukopenia, and elevated aminotransferase levels are common in *R parkeri* infection.¹ Both infections appear to be milder than RMSF.

Diagnosis of the specific infection is challenging due to the cross-reactivity of SFGR serologic tests. Additional testing with PCR, immunohistochemistry, and culture at specialized laboratories may aid in diagnosis. Because RMSF cannot be ruled out, all cases of SFGR should be treated the same as *R rickettsii* with a course of doxycycline.¹⁷

■ EHRlichIOSES: EHRlichIOSIS AND ANAPLASMOSIS

“Ehrlichiosis” is the generic name for infections caused by both the *Ehrlichia* and *Anaplasma* genera,^{19,20} which are small, gram-negative obligate intracellular bacterial pathogens.²¹ In the United States, infections are most commonly caused by *A phagocytophilum*, the causative organism of human granulocytic anaplasmosis (HGA) (Table 4), and *E chaffeensis*, the causative organism of human monocytic ehrlichiosis (HME) (Table 5). The incidence rates of these 2 infections have increased over the past decade, in part due to increased clinical

awareness and improved diagnostic capabilities.^{3,22,23}

E ewingii (Table 6) and *E muris*-like agent (Table 7) are lesser known causes of human ehrlichiosis in the United States.^{20,23–25} Initially, *E ewingii* was believed to primarily affect immunocompromised patients, but it was later recognized in immunocompetent hosts.²³ *E muris*-like agent was first discovered as a cause of infection in 2009, and cases have been limited to Wisconsin and Minnesota.^{24,25}

Human granulocytic anaplasmosis. *A phagocytophilum* is transmitted by *Ixodes scapularis* (the deer tick or blacklegged tick) in the northeastern and upper-midwestern regions of the United States, and *I pacificus* (the western blacklegged tick) along the northern Pacific coast.^{1,19,20,26} The 6 states accounting for most cases are New York, Connecticut, Massachusetts, Rhode Island, Minnesota, and Wisconsin.²⁷ The white-footed mouse serves as the primary reservoir for *A phagocytophilum*, and humans are an accidental, “dead-end” host.²¹ Cases have also been reported to be transmitted via blood transfusion and transplacentally.^{20,26,28,29}

Human monocytic ehrlichiosis. *E chaffeensis* is transmitted by *Amblyomma americanum* (the Lone Star tick).²⁰ It is most commonly found in the southeastern, south-central, and mid-Atlantic regions of the United States.^{19,20,30} The 5 states with the most cases are Missouri, Oklahoma, Tennessee, Arkansas, and Maryland.^{1,4,27} White-tail deer are the primary reservoir for *E chaffeensis*.

Treatment
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is suspected

TABLE 4

Human granulocytic anaplasmosis**Pathogen:** *Anaplasma phagocytophilum***Tick vectors:** *Ixodes scapularis*, *Ixodes pacificus***Geographic distribution:** Northeast and upper Midwest, northern Pacific coast**Classic presentation:** Fever, headache, myalgia, malaise, cough, opportunistic infections in severe cases, thrombocytopenia, leukopenia, lymphopenia, elevated aminotransferase levels; laboratory abnormalities may no longer be present after 1 week of symptoms**Diagnosis:** Polymerase chain reaction assay available; 4-fold increase between acute and convalescent serology with a minimum peak titer $\geq 1:64$; morulae in granulocytes on Giemsa- or Wright-stained peripheral smear; cell culture rarely used**Treatment:** Doxycycline, typically for 10 days (range 7–14 days)

TABLE 5

Human monocytic ehrlichiosis**Pathogen:** *Ehrlichia chaffeensis***Tick vectors:** Primarily *Amblyomma americanum***Geographic distribution:** Southeastern, south-central, and mid-Atlantic regions**Classic presentation:** Fever, headache, myalgia, malaise, cough, gastrointestinal symptoms, rash, meningitis, thrombocytopenia, leukopenia, lymphopenia, anemia, hyponatremia, elevated aminotransferase levels; laboratory abnormalities may no longer be present after 1 week of symptoms**Diagnosis:** Polymerase chain reaction assay available; 4-fold increase between acute and convalescent serology with a minimum peak titer $\geq 1:64$; morulae in monocytes on Giemsa- or Wright-stained peripheral smear; cell culture rarely used**Treatment:** Doxycycline, typically for 7–14 days**Clinical manifestations of ehrlichiosis**

After an incubation time of 5 to 21 days, ehrlichiosis typically presents as a febrile viral-like illness with nonspecific symptoms that include fever, chills, sweats, myalgia, headache, malaise, and cough.^{1,26,27,31}

Gastrointestinal symptoms, arthralgia, photophobia, and nervous system involvement may also occur.^{1,20,29,32} Gastrointestinal symptoms tend to be more common in HME than HGA.²⁰

Rash occurs in up to one-third of patients with HME, but it is rare in HGA.^{4,19,20,27} HME presents with more central nervous system involvement (such as meningitis or seizures) than HGA, in which central nervous system involvement is rare.

Severe complications of HME and HGA occur in a minority of cases and may include acute respiratory distress syndrome, renal failure, disseminated intravascular coagulopathy, and spontaneous hemorrhage.¹⁹ In general, HME is more severe than HGA and is more likely to progress to fulminant toxic or septic shocklike syndrome in rare instances.¹⁹

Laboratory tests may reveal leukopenia,

lymphopenia, thrombocytopenia, and elevated liver-associated enzyme levels.^{1,19,20,26} Anemia and hyponatremia may also be present.^{4,30}

Diagnosis of ehrlichiosis

The most rapid diagnostic method is examination of Wright- or Giemsa-stained peripheral blood smears for morulae, which are cytoplasmic intravacuolar inclusions of bacteria within leukocytes.²⁰ However, its sensitivity is as low as 20% and declines even further after the first week of infection.^{4,20}

PCR testing is the most sensitive and rapid tool available during acute infection.^{1,20,26,30,31} However, due to waning of the bacteremic phase, its sensitivity decreases after the first week of infection and after treatment is started.^{19,20}

Serologic detection of antibodies with an indirect immunofluorescence assay is the most frequently used test for diagnosis of ehrlichiosis, and paired serology demonstrating seroconversion (at least a 4-fold increase in titer, with a minimal titer of 1:64) is most sensitive (82% to 100%).^{4,19,20,26} Cross-reactivity can occur, so testing for antibodies to both *A phagocytophilum* and *E chaffeensis* might assist

Ehrlichiosis is the generic name for infections caused by both the *Ehrlichia* and *Anaplasma* genera

TABLE 6

Human *Ewingii* ehrlichiosis

Pathogen: *Ehrlichia ewingii*

Tick vector: Primarily *Amblyomma americanum*

Geographic distribution: Southeastern and south-central regions

Classic presentation: Similar to human granulocytic anaplasmosis and human monocytic ehrlichiosis; laboratory abnormalities may no longer be present after 1 week of symptoms

Diagnosis: Polymerase chain reaction assay

Treatment: Doxycycline, typically for 7–14 days

TABLE 7

Ehrlichia muris-like agent infection

Tick vector: *Ixodes scapularis* (most likely)

Geographic distribution: Limited to Wisconsin and Minnesota

Classic presentation: Similar to human granulocytic anaplasmosis and human monocytic ehrlichiosis; laboratory abnormalities may no longer be present after 1 week of symptoms

Diagnosis: Polymerase chain reaction assay

Treatment: Doxycycline, typically for 7–14 days

in a more accurate diagnosis in areas where tick vectors overlap.^{4,19,20,26}

HGA and HME can be isolated through cell culture in blood or cerebrospinal fluid. However, this is labor-intensive and performed in only a few specialized laboratories.^{4,19,20,27,31}

Treatment of ehrlichiosis

If ehrlichiosis is suspected, treatment should not be delayed; the disease can be life-threatening and the ability to diagnose acute infection is often limited.^{20,26,32}

Doxycycline is the treatment of choice, even in pregnant patients with severe infection and in children.^{1,19,26,27} Antibiotics are given for 5 to 10 days and continued for at least 3 days after the fever subsides.^{19,20,26,27,30} In HGA, a 10-day course of doxycycline is recommended to also provide the appropriate length of treatment for *Borrelia burgdorferi*.^{1,31}

Rifampin is an alternative for those with severe tetracycline allergy, as well as those with mild to moderate infection during pregnancy.^{1,20,26,29–32}

Fever typically resolves within 24 to 48 hours of starting treatment, and persistence of fever over 48 hours after starting antibiotics suggests an alternative diagnosis or possible coinfection.^{1,4,19,20,26,27,30,32}

Persistence of chronic *A phagocytophilum* or *E chaffeensis* infection in humans beyond 2 months has not been demonstrated.^{20,26,30,33} Therefore, antibiotic treatment beyond the

acute stage of infection is not indicated.³⁰ Long-term prognosis is favorable, and patients are expected to make a full recovery.^{26,30}

■ BABESIOSIS

Babesiosis (Table 8) is a malaria-like illness caused by intraerythrocytic protozoan parasites of the genus *Babesia*. Most cases in the United States are caused by *Babesia microti*.

Babesiosis occurs in the northeastern and upper midwestern states, with most cases reported in Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Minnesota, and Wisconsin.^{31,32,34–36} Outbreaks have also been documented in Washington, California, and Missouri.^{31,32,35} The spread mimics that of Lyme disease, though it can be slower.^{34,36–39}

Most cases in the Northeast and upper Midwest are caused by *Babesia microti*, while *Babesia duncani* has sporadically caused disease along the Pacific coast and *Babesia divergens* has been found in the Midwest and Northwest.^{34,36,39}

Though babesiosis is usually a tickborne illness, it can also be transmitted through blood transfusion and, rarely, transplacental spread.^{31,32,34,36,39–41} The *I scapularis* tick is the host vector for *Babesia microti*, and transmission of disease requires 24 to 72 hours of attachment to a host.^{34,35} The primary reservoir for *Babesia microti* is the white-footed mouse, and humans are accidental hosts.^{32,34–36,39}

If ehrlichiosis is suspected, treatment should not be delayed

Clinical manifestations of babesiosis

Babesia species cause illness by lysing erythrocytes, with resultant cytokine release.³⁴

Symptoms typically appear 1 to 4 weeks after inoculation, after which most cases present as a viral-like illness with gradual onset of fever, chills, sweats, fatigue, malaise, headache, arthralgia, myalgia, nausea, anorexia, and nonproductive cough.^{32,34–36,39}

Physical findings may include splenomegaly, hepatomegaly, jaundice, petechiae, and ecchymosis.^{32,34–36,39} Rash is seldom present and is not a characteristic feature of babesiosis.^{35,36}

Laboratory features may include thrombocytopenia, hemolytic anemia, and elevated liver enzyme levels.^{32,34,36,39}

Severe disease can occur in elderly, immunocompromised, or splenectomized individuals and can be life-threatening.^{34,39} Complications of severe infection can include acute respiratory distress syndrome, diffuse intravascular coagulation, and liver or renal failure.^{31,32,34–36,39} Splenic infarction or rupture may occur at lower levels of parasitemia in those without other manifestations of severe disease.³¹ The course can be prolonged and relapsing despite standard antibiotic therapy, typically in the setting of severe immunocompromise.^{32,34,42,43} Death occurs in up to 10% of severe cases.³⁴

Diagnosis of babesiosis

Babesiosis should be considered if a patient presents with a febrile illness and nonspecific symptoms and comes from an endemic area or has received a blood transfusion within 6 months.^{34,35}

The diagnosis of babesiosis is most commonly made by finding the intraerythrocytic ring form of the organism (trophozoite) on Giemsa- or Wright-stained thin blood smears.^{34,36,39} *Babesia* can be distinguished from *Plasmodia* (the agent of malaria) by the rare presence of tetrads of merozoites arranged in a cross-like pattern (the Maltese cross); the absence of hemozoin (brownish deposits) in the ring form; and the occasional presence of extracellular ring forms.^{34,36}

The level of parasitemia (representing the number of parasites per microliter of blood) is generally between 1% and 10%, although it can be as high as 80%.^{36,39} Because parasitemia

TABLE 8

Babesiosis

Pathogen: *Babesia microti* (most likely)

Tick vector: *Ixodes scapularis*

Geographic distribution: Northeastern region and upper-midwestern states

Classic presentation: Fever, fatigue, malaise, headache, myalgia, arthralgia, nausea, anorexia, cough, hemolytic anemia, thrombocytopenia, leukopenia, elevated aminotransferase levels

Diagnosis: *Babesia microti* intraerythrocytic ring form (trophozoites) or merozoites in tetrads (Maltese cross) identified on Giemsa- or Wright-stained peripheral smear; polymerase chain reaction assay; serology

Treatment: Atovaquone with azithromycin for mild to moderate disease and clindamycin with quinine for severe disease; consider exchange transfusion in severe disease; typical treatment course is 7–10 days and at least 6 weeks in highly immunocompromised patients

is often low early in disease (< 1%), multiple blood smears should be examined.^{34–36,39}

Several real-time PCR assays are available to detect low-grade *Babesia microti* parasitemia in patients with negative blood smears during early infection.³¹ These assays have high diagnostic sensitivity and specificity and do not cross-react with other *Babesia* or *Plasmodium* species.^{34–36,39}

Paired serology (immunoglobulin G) can confirm infection, although antibody may be absent early in the course of illness.^{31,34–36,39}

Treatment of babesiosis

Current guidelines recommend antimicrobial therapy only for patients with symptoms and positive test results for *Babesia*.³² Treatment of asymptomatic patients should additionally be considered if parasitemia (not positive PCR or serology) persists for 3 months or longer.^{32,34–36,39}

For mild to moderate babesiosis, the combination of oral atovaquone and azithromycin for 7 to 10 days has similar efficacy and a lower incidence of adverse effects than clindamycin plus quinine.^{31,32,34,44} For immunocompromised

Babesiosis is a malaria-like illness caused by protozoan parasites in red blood cells

TABLE 9

Tickborne relapsing fever**Pathogen:** *Borrelia hermsii***Tick vectors:** *Ornithodoros hermsi*; less commonly *Ornithodoros parkeri* and *Ornithodoros turicata***Geographic distribution:** Pacific coast, northwestern and southwestern regions**Classic presentation:** Relapsing fever, headache, myalgia, arthralgia, gastrointestinal symptoms**Diagnosis:** Detection of spirochetes on peripheral smear with either Wright or Giemsa stain or darkfield microscopy; fourfold increase between acute and convalescent serology with a minimum peak titer $\geq 1:64$; polymerase chain reaction assay in research settings.**Treatment:** Tetracycline for 10 days (based on expert opinion)

TABLE 10

Borrelia miyamotoi* infection*Tick vectors:** *Ixodes scapularis*, *Ixodes pacificus***Geographic distribution:** Northeastern, north-central, and far western regions**Classic presentation:** Fever, headache, myalgia, arthralgia, gastrointestinal symptoms, meningoencephalitis, thrombocytopenia, elevated aminotransferase levels**Diagnosis:** No validated test available, though culture, polymerase chain reaction, and serology are performed in research settings**Treatment:** Doxycycline for 2–4 weeks (based on expert opinion)

Consider exchange transfusion for patients with a high level of parasitemia, severe anemia, or with renal, hepatic, or pulmonary compromise

patients, higher doses of azithromycin can be used.^{31,32}

For severe babesiosis or those with risk factors for severe disease, intravenous clindamycin and oral quinine are recommended for 7 to 10 days based on expert opinion.^{31,32,34–36,39,43} Adverse effects of this regimen include diarrhea, tinnitus, and hearing deficits.^{35,39} If necessary, intravenous quinidine can be used, but the patient should receive cardiac monitoring for possible prolongation of the QT interval.^{34,39} As quinine therapy is often interrupted due to the above side effects, alternative regimens such as intravenous azithromycin or clindamycin in combination with oral atovaquone should be considered for severe cases.³¹ However, these regimens are not well studied.³¹

Partial or complete exchange transfusion of whole blood or packed red blood cells should be considered in patients with a high level of parasitemia ($\geq 10\%$), severe anemia (hemoglobin < 10 g/dL), or renal, hepatic, or pulmonary compromise.^{31,32,34–36,39} In critically ill patients, parasitemia should be monitored daily until it has decreased to less than 5%.^{32,34,39}

Generally, symptoms improve within 48 hours of antimicrobial therapy initiation;

however, parasitemia may take up to 3 months to resolve.^{32,34,39} In severely immunocompromised patients, babesiosis may persist or relapse despite appropriate therapy.^{34,39,42,43} In these cases, at least 6 weeks of antimicrobial therapy is recommended, including 2 weeks of therapy after *Babesia* organisms are no longer seen on blood smear.^{31,33,36,39,42}

■ TICKBORNE RELAPSING FEVER

Relapsing fever, as the name implies, is characterized by recurring episodes of fever and nonspecific flulike symptoms (Table 9).

The illness is transmitted by either ticks or body lice. The tick-borne illness is caused by spirochetes of the genus *Borrelia* and transmitted to humans by the bite of an infected *Ornithodoros* soft tick.⁴⁵ Approximately 70% of reported cases in the United States occur in California, Washington, and Colorado.⁴⁶ Most cases are caused by *Borrelia hermsii* and are linked to sleeping in rodent-infested cabins in mountainous areas.⁴⁶ Remarkably, tick-borne borreliae are transmitted within about 30 seconds of tick attachment.^{47,48}

The hallmark of tickborne relapsing fever is febrile episodes lasting 3 to 5 days, with relapses after 5 to 7 days of apparent recovery.⁴⁹ If untreated, several episodes of fever and non-

specific symptoms will occur before illness resolves spontaneously. Overall mortality rates are very low (< 5%).⁵⁰

Laboratory confirmation of tickborne relapsing fever is made by detecting spirochetes in a blood smear during a febrile episode or serologic antibody confirmation. However, serologic testing is unhelpful in the acute setting and can yield false-positive results with prior exposure to other *Borrelia* species (eg, Lyme disease) or other spirochetes. Serologic antibody testing with a 4-fold increase between acute and convalescent samples or PCR can aid in diagnosis, though the latter is available only in research settings.⁴⁷

The preferred treatment regimen for adults is an oral tetracycline for 10 days. Erythromycin is recommended when tetracyclines are contraindicated.⁵¹

When starting treatment, all patients should be monitored closely for the Jarisch-Herxheimer reaction (rigors, hypotension, and high fevers), which develops in over 50% of cases as a result of rapid spirochetal killing and massive cytokine release.⁵²

■ BORRELIA MIYAMOTOI INFECTION

Borrelia miyamotoi (Table 10) is a spirochete closely related to those causing tickborne relapsing fever, recently identified as a human pathogen and transmitted by the same tick species that transmit Lyme disease—*I pacificus* ticks in the far western United States and *I scapularis* in northeastern and north-central United States. The reservoir hosts are poorly known, but the organism has been detected in small rodents as well as birds and larger animals.^{53,54}

The most common clinical manifestations are similar to other tickborne relapsing fever infections, although a true “relapsing fever” itself is not usually present.⁵³ The characteristic erythema migrans rash often found in Lyme disease is typically absent in *B miyamotoi* infection; however, when present, it should prompt investigation into coinfection.⁵⁴ Cases of meningoencephalitis have been reported in immunosuppressed hosts.⁵⁵

There is currently no validated test available for diagnosis of *B miyamotoi*; however, PCR and serology are available in a few specialized laboratories.^{31,53}

TABLE 11

Southern tick-associated rash illness

Pathogen: Unknown

Tick vector: *Amblyomma americanum*

Geographic distribution: Southeastern, south-central, mid-Atlantic, and midwestern regions

Classic presentation: Fever, headache, fatigue, myalgia, erythema migrans rash (similar to Lyme disease)

Diagnosis: No diagnostic tests are available since the pathogen is unknown; diagnosis based on symptoms, geographic location, and possibility of a tick bite; a known tick bite by *A americanum* is helpful in distinguishing from Lyme disease.

Treatment: Doxycycline is often given, though it is unknown whether antibiotics are necessary or beneficial

The treatment of choice is doxycycline for 2 to 4 weeks. Amoxicillin and ceftriaxone also appear effective.⁵³

■ SOUTHERN TICK-ASSOCIATED RASH ILLNESS

Southern tick-associated rash illness (STARI) (Table 11) is associated with the bite of the Lone Star tick, *A americanum*. Most cases are diagnosed in the southeastern and south-central United States where the tick is endemic; however, its range is expanding. It was originally speculated that *Borrelia lonestari* caused STARI, though more recent evidence has not supported this.⁵⁶ At this time, the cause of STARI is unknown.

Infection can present similarly to Lyme disease with an erythema migrans-like rash and associated flulike symptoms, although systemic symptoms and multiple erythema migrans lesions are less likely with STARI. Also, the erythema migrans-like lesions tend to be smaller and more likely to have central clearing than those in Lyme disease.⁵⁷ Nevertheless, it is difficult to distinguish the 2 illnesses, especially in mid-Atlantic states such as Maryland or Virginia, where both diseases coexist. The most reliable method of distin-

**STARI
can present
similarly
to Lyme disease**

TABLE 12

Tularemia**Pathogen:** *Francisella tularensis***Tick vectors:** *Amblyomma americanum*,
Dermacentor variabilis, *Dermacentor andersoni***Geographic distribution:** South-central region**Classic presentation:**Ulceroglandular: Red painful papule at the site of tick exposure that evolves into a black eschar; fever, headache, myalgia, malaise, lymphadenopathy
Glandular: Same as ulceroglandular except primary lesion not recognized**Diagnosis:** 4-fold increase between the acute and convalescent sera or a single titer $\geq 1:160$; culture may also be performed**Treatment:** Streptomycin or gentamicin for at least 10 days; for less severe disease, ciprofloxacin or doxycycline for 14 days

Francisella tularensis is one of the most virulent bacteria known

guishing STARI from Lyme disease is demonstrating that the patient was bitten by a Lone Star tick rather than an *Ixodes* tick. Numerous questions remain unanswered about the causative organism, pathophysiology, definitive diagnosis, geographic range of illness, and most effective treatment for STARI.

Most reported cases have responded promptly to doxycycline, though it is not known whether antibiotic treatment is necessary.⁵⁸

■ TULAREMIA

Tularemia (Table 12) is a zoonotic infection caused by the gram-negative bacterium *Francisella tularensis*. The organism is one of the most virulent bacteria currently known; the high rate of infectivity has led to its classification as a category A biowarfare agent. *F tularensis* infects more than 200 species of animals and invertebrates.

Ticks are thought to be the most important vectors, and most cases occur in the south-central United States.⁵⁹ The geographic distribution of disease is gradually shifting northward due to spread of the major tick vectors, *A americanum*, *D variabilis*, and *D andersoni*. Approximately 100 to 200 cases of tularemia

TABLE 13

Powassan virus infection**Tick vectors:** Lineage I: *Ixodes cookei*; lineage II (also known as deer tick virus): *Ixodes scapularis***Geographic distribution:** Great Lakes and northeastern regions**Classic presentation:** Fever, confusion, seizures, focal neurologic deficits, rash, gastrointestinal symptoms**Diagnosis:** Cerebrospinal fluid testing for virus-specific IgM and neutralizing antibodies; serum antibody testing; nucleic acid amplification; immunohistochemistry on autopsy tissue and viral culture are options**Treatment:** Supportive care

are diagnosed each year in the United States, with most concentrated in Kansas, Oklahoma, Missouri, and Arkansas.⁶⁰

Humans can acquire *F tularensis* by several routes, and the route of infection ultimately dictates the clinical syndrome. Ulceroglandular and glandular forms of the disease are the most common in the United States, and both frequently result from a tick bite. A few days after tick exposure, an erythematous, often painful papuloulcerative lesion with a central eschar manifests at the site of the tick bite. Additional symptoms may include fever, chills, headache, myalgia, malaise, and suppurative lymphadenitis.⁶¹

Diagnosis can be made by identifying *F tularensis* in blood, fluid, or tissue culture performed under biosafety level 3 conditions; however, serology is used in most cases.⁶²

Streptomycin and gentamicin are considered drugs of choice and should be continued for at least 10 days. For relatively mild disease, oral doxycycline or ciprofloxacin can be considered for at least 14 days, although the latter is not approved for treatment.^{59,63}

■ TICKBORNE VIRAL INFECTIONS

While most arboviruses are transmitted by mosquitoes, 2 tickborne viruses can cause infection in specific regions of the United

States: Powassan virus (Table 13) and Heartland virus (Table 14).

Powassan virus, an uncommon flavivirus, is found in the Great Lakes region and north-east United States. In the Great Lakes region, *I cookei* ticks transmit the traditional lineage of this virus. However, more recent cases have been identified in the Northeast and Midwest, where Powassan virus lineage II (or deer tick virus) is transmitted by *I scapularis*.^{31,64}

The classic presentation is a viral encephalitis. Rash (most often maculopapular) and gastrointestinal symptoms have been reported as well. A high index of suspicion is needed for diagnosis because clinical features and laboratory findings resemble those of other arboviral infections.

Treatment for Powassan viral encephalitis is supportive, although corticosteroids have been used with some success.⁶⁴ While asymptomatic infection has been documented, the reported mortality rate of Powassan virus encephalitis is 10% to 15%, and focal neurologic deficits can persist among survivors.⁶⁵

Heartland virus is a newly identified phlebovirus that has been reported only in rural Missouri and Tennessee to date. Infection is presumed to be transmitted by *A americanum*.⁶⁶ An animal reservoir has not been established.

Clinical and laboratory features appear to be very similar to those of the ehrlichioses.¹ A clinical diagnosis should be considered in patients with *A americanum* exposure, fever, and cytopenias who lack PCR or serologic evidence for ehrlichiosis infection or who fail to respond to doxycycline therapy.²⁴

COINFECTION

Some tick vectors transmit more than 1 type of infection, and therefore, coinfection with multiple pathogens may occur. For example, *I scapularis* transmits *Borrelia burgdorferi* (Lyme disease), HGA, *Babesia microti*, *B miyamotoi*, *E muris*-like agent, and Powassan virus lineage II, while *A americanum* transmits HME and Heartland virus.^{24,26,31,34,36,67} Coinfection may increase the severity of disease, often due to a delay in diagnosis, though more research is needed to understand the clinical manifestations of coinfection.^{31,35,67}

TABLE 14

Heartland virus infection

Tick vector: *Amblyomma americanum* (most likely)

Geographic distribution: Limited to Missouri and Tennessee

Classic presentation: Fever, fatigue, headache, myalgia, gastrointestinal symptoms, leukopenia, thrombocytopenia

Diagnosis: No diagnostic tests are currently available; rule out ehrlichioses

Treatment: Supportive care

PREVENTION

Unfortunately, there are no available human vaccines for tickborne illnesses in the United States, and the effectiveness of single-dose prophylaxis with doxycycline for non-Lyme infections has not been evaluated.^{4,7,26}

Illness is best prevented by minimizing skin exposure to ticks, use of tick repellents containing DEET, use of long-legged and long-sleeved clothing impregnated with an acaricide such as permethrin, and conducting timely body checks for ticks after potential exposure.^{1,31,32} Light-colored clothing is suggested, since it allows for better visibility of crawling ticks.^{4,32} Bathing or showering within 2 hours of tick exposure helps prevent attachment of ticks.^{4,31,68} If camping outside, use of a bed net is recommended.⁶⁸

Ticks are most easily removed by grasping the head of the tick as close to the skin surface as possible with fine-tipped tweezers.^{32,68} Removing or crushing ticks with bare hands should be avoided to prevent potential contamination, and hands should be washed thoroughly after tick removal.^{1,4}

Blood donors are screened for a history of symptomatic tickborne disease; however, asymptomatic donors who are not identified at screening pose the greatest risk to the blood supply. *Babesia microti* is the most common reported transfusion-transmitted parasite in the United States, and transmission of *R rickettsii*, *A phagocytophilum*, and *E ewingii* have also

Illness is best prevented by minimizing skin exposure to ticks

been reported infrequently.^{28,40,69} Currently, no test is approved to screen blood for tickborne illnesses, though such a test would help prevent transmission of tickborne illnesses by blood transfusion in areas where these diseases are endemic.^{40,41}

■ TAKE-HOME POINTS

Tickborne illnesses are increasing throughout the United States as a result of vector expansion and changes in human ecology.

It is essential that primary care clinicians consider tickborne illnesses in the differential diagnosis for any patient presenting with a fever and constitutional symptoms when the cause of symptoms is unclear and tick exposure is possible or known.

All the diseases discussed are nationally notifiable conditions, and confirmed cases should be reported.

Knowledge of the geographic locations of potential exposure is paramount to determining which tickborne infections to consider, and the absence of a tick bite history should not exclude the diagnosis in the correct clinical presentation.

In addition, it is important to recognize the limitations of diagnostic testing for many tickborne infections; empiric treatment is most often warranted before confirming the diagnosis.

Tick avoidance is the most effective way to prevent these often severe infections. ■

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