Tickborne Diseases in Children in the United States

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Practice Gaps

The most common tick-borne infections in the United States are Lyme disease, ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever, and babesiosis. The epidemiology of these infections in the United States is integrally related to the geographic distribution and seasonality of the tick vector of each of the infections. Because these infections can be very serious and sometimes fatal, and because of the inherent delay in obtaining laboratory confirmation (especially with serologic assays requiring acute and convalescent titers), considering early implementation of empirical treatment based on the patient’s clinical presentation is extremely important. Prevention of acquisition of tick-borne diseases requires avoiding tick-infested areas or, if this is not possible or desired, implementing steps to decrease the likelihood of tick bites and the duration of tick attachment.

Objectives

After completing this article, readers should be able to:

1. Understand the etiologic organisms and the associated ticks responsible for transmission, the geographic distribution of and the reported infections associated with the ticks in the United States, and the seasonality and incubation periods of tick-borne infections in the United States.

2. Recognize the clinical manifestations and laboratory abnormalities associated with the infections, especially as they relate to children.

3. Plan for the diagnosis, treatment, and prevention of these infections.

INTRODUCTION

Vector-borne diseases, caused by microorganisms transmitted by insects and ticks, are major causes of morbidity and mortality globally. In the United States, vector-borne diseases are occurring more frequently and represent a significant public health concern. (1) The numbers of reported vector-borne disease cases in the United States (tick-borne, mosquito-borne, and flea-borne diseases) are

AUTHOR DISCLOSURE

Dr Read has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CSF cerebrospinal fluid
EM erythema chronicum migrans
IFA immunofluorescent antibody
Ig immunoglobulin
RMSF Rocky Mountain spotted fever
PCR polymerase chain reaction
shown in Table 1. (1) The reported incidence of vector-borne
diseases most likely significantly underestimates the actual
occurrence of these diseases; some individuals with vector-
borne infections may be asymptomatic or, if symptomatic,
may not seek medical care.

This review addresses the most common tick-borne
diseases reported in the United States, (1) specifically, Lyme
disease, ehrlichiosis and anaplasmosis, spotted fever rickettsiosis,
including Rocky Mountain spotted fever (RMSF),
and babesiosis. Specifically, the following are discussed: the
organisms and the associated ticks responsible for trans-
mission; the geographic distribution of and the reported
infections associated with the ticks in the United States;
the seasonality of tick-borne infections in the United States;
the infections’ incubation periods; the clinical manifest-
tations and laboratory abnormalities associated with the
infections, especially as they relate to children; and the
diagnosis, treatment, and prevention of these infections.

**LYME DISEASE**

Lyme disease is the most common tick-borne infection in
the United States. (2) Over a 12-year period ending in 2016,
402,502 cases of Lyme disease were reported in the United
States. (1) Table 2 summarizes characteristics of *Borrelia
burgdorferi* sensu stricto (*B burgdorferi*), the causative organ-
ism of Lyme disease in the United States. The first report in
the United States of the skin lesion characteristic of Lyme
disease, erythema chronicum migrans (EM), was published
in 1970. (3) Subsequently, the full spectrum of clinical
manifestations of Lyme disease, including EM, was
described in 1977. (4) *B burgdorferi*, a spirochete in the
family Spirochaetaceae, (5) was first isolated in 1982. (6)
Another *Borrelia* species (*Borrelia miyamotoi*) was first iden-
tified in Japan in the 1990s, (7) and subsequently the first
case in the United States was described. (8)

*B burgdorferi* infection is transmitted by the blacklegged
tick (*Ixodes scapularis*) (Fig 1) and the western blacklegged
tick (*Ixodes pacificus*). (2) *B miyamotoi* is transmitted by the
same tick vectors as *B burgdorferi*. (9)(10)(11)(12) The season-
ality of Lyme disease is summarized in Table 2. (5) In the
United States, most cases of Lyme disease are reported from
2 regions: 1) New England through the mid-Atlantic states
and 2) the upper Midwest states (Table 2, Fig 2). (5)(13) *B
miyamotoi* infections have similar seasonality and distribu-
tion as Lyme disease cases. (9)(10)(12)

The incubation period and clinical manifestations of, and
the laboratory abnormalities associated with, Lyme disease
are summarized in Table 3. (2)(5)(13) The clinical manifest-
ations of Lyme disease occur in 3 stages: early localized,
early disseminated, and late. (5) Early localized disease
(2)(5)(13) is characterized by EM at the site of the tick bite
and systemic manifestations. In children, EM is the most
common manifestation of Lyme disease. Some patients with
large EM lesions are misdiagnosed as having cellulitis. Only
a minority of patients have the classic bull’s-eye appearance
(concentric rings). Several weeks after the tick bite, the next
stage of Lyme disease (early disseminated disease) (2)(5). (13)
may manifest as multiple EM lesions. Other clinical manifestations may occur (with or without multiple EM lesions), including neurologic, cardiac, and systemic manifestations. Late Lyme disease (2)(5)(13) occurs in individuals who were not treated during the early localized or early disseminated stages of infection. Several months may pass between a tick bite and late Lyme disease manifestations. Children with late Lyme disease usually present with arthritis. Because some patients with Lyme disease do not report a history of clinical features of early localized or early disseminated
Lyme disease, arthritis and other manifestations of late Lyme disease may occur in patients without a history of EM. Patients with \textit{B. miyamotoi} infections most commonly report systemic manifestations (fatigue, headache, arthralgia, myalgia, nausea) as well as high fever (temperature $>104^\circ\text{F}$ [$>40^\circ\text{C}$]), which may be recurrent, and chills. Laboratory abnormalities observed in patients with Lyme disease include an elevated erythrocyte sedimentation rate, elevated hepatic transaminase concentrations, and microscopic hematuria or proteinuria. With Lyme meningitis, the cerebrospinal fluid (CSF) usually has a lymphocytic pleocytosis, a slightly elevated protein concentration, and a normal glucose concentration. Leukopenia, thrombocytopenia, and elevated liver enzyme concentrations have been reported with \textit{B. miyamotoi} infection.

![Figure 1. Ticks that commonly bite humans. (Reprinted with permission from Centers for Disease Control and Prevention. Tickborne Diseases of the United States. 5th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2018.)](image)

Diagonalic assays for Lyme disease are summarized in Table 4. Of note, the diagnosis of Lyme disease depends heavily on a compatible clinical presentation along with plausible geographic exposure to the tick vector. Patients with early Lyme disease with EM may be treated presumptively (and serologic testing is not recommended). The laboratory diagnosis of Lyme disease involves demonstration of \textit{B. burgdorferi} antibodies in serum. A 2-step laboratory testing protocol is recommended. First, an enzyme-linked immunosorbent assay or an immunofluorescent antibody (IFA) assay is performed. If the result of the antibody assay is positive or equivocal, the second-tier standardized Western immunoblot is necessary. If Lyme meningitis is suspected, the CSF can be tested for immunoglobulin (Ig) M or IgG antibodies. There are several important considerations for serologic testing for Lyme disease. First, antibody titers are often negative if the serum specimen was obtained during the first few weeks of infection. Second, in those with more than 1 month of illness, only IgG testing should be performed (not IgM testing). Third, because of antibody persistence, a single positive serologic assay result cannot reliably distinguish between previous and current infection. Fourth, serologic assays cannot be used to assess response to treatment. Fifth,
and most importantly, serologic assays may yield false-positive results; there may be cross-reactivity with antibodies to other spirochetes and to certain viruses (including Epstein-Barr virus and varicella) and there may be false-positive results in patients with certain autoimmune diseases (eg, systemic lupus erythematosus). It is, therefore, important to perform Lyme disease testing with an appropriate epidemiologic history of potential contact with tick vectors associated with transmitting Lyme disease and compatible clinical manifestations. The laboratory diagnosis of *B. miyamotoi* infection can be accomplished by identification of the spirochetes on blood smears or CSF samples (if neurologic manifestations), through polymerase chain reaction (PCR) assays performed on blood or CSF samples, and with serologic assays. (19)

Treatment of Lyme disease is summarized in Table 4. (5)(13) Antibiotic therapy for patients who are asymptomatic (but seropositive) or who have nonspecific symptoms is not recommended. As noted previously herein, patients with EM can be treated presumptively. *B. miyamotoi* infections can be treated with doxycycline or amoxicillin. (20)

**EHRlichiosis AND Anaplasmosis**

Between 2004 and 2016, 39,959 cases of ehrlichiosis and anaplasmosis were reported in the United States (1) Table 2 summarizes characteristics of the causative organisms. Ehrlichiosis and anaplasmosis are caused by infections with Gram-negative cocci of the family Anaplasmataceae, which are obligate intracellular bacteria. (21)(22)(23)(24) In the United States, ehrlichiosis is caused by 1 of 3 different species of *Ehrlichia* (*Ehrlichia chaffeensis*, *Ehrlichia ewingii*, and *Ehrlichia muris eauclairesis*). *E. chaffeensis*, first described in 1987, is the most common cause of human ehrlichiosis in the United States. (25) The other species of *Ehrlichia* were recognized in the 1990s. (26)(27) Anaplasmosis in the United States is caused by *Anaplasma phagocytophilum* and was first described in humans in the 1990s. (28) These organisms have a tropism for leukocytes (*Ehrlichia* species: usually monocytes or tissue macrophages; *A. phagocytophilum*: usually granulocytes). (21)(22)(23)(24)

Both *Ehrlichia* species and *A. phagocytophilum* are transmitted by ticks, but *A. phagocytophilum* also can be transmitted
<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INCUBATION PERIOD</th>
<th>CLINICAL MANIFESTATIONS</th>
<th>LABORATORY ABNORMALITIES</th>
</tr>
</thead>
</table>
| Lyme disease | 3–32 d (median, 11 d) | Early localized stage:  
  - EM rash:  
    - Begins with a red macule or papule, which subsequently (over a period of days to weeks) expands to form a large, erythematous, annular lesion, with or without central clearing  
    - Usually painless (but not always) and usually nonpruritic  
    - Variable in terms of size and shape (size usually >5 cm)  
    - May have a central vesicular component, purplish discoloration, or necrosis  
  - Systemic manifestations: fever (usually mild), malaise, headache, myalgia, arthralgia  
Early disseminated stage:  
  - Multiple EM lesions (similar to but smaller than primary lesion)  
  - Other manifestations (with or without EM lesions):  
    - Cranial nerve palsies (usually cranial nerve VII)  
    - Lymphocytic meningitis (often with papilledema or cranial neuropathy)  
    - Radiculitis  
    - Carditis (atrioventricular block of varying degree)  
      (occurs less commonly in children)  
  - Systemic manifestations: fever (usually mild), fatigue, headache, myalgia, arthralgia  
Late disseminated stage:  
  - Arthritis (usually monoarticular or pauciarticular, affecting large joints [especially knees])  
  - Other rare manifestations:  
    - Pseudotumor cerebri  
    - Encephalitis  
    - Encephalopathy  
    - Polynuropathy  |
| Ehrlichiosis | 5–14 d | Systemic manifestations: fever, chills, malaise, headache, myalgia, nausea  
  - Gastrointestinal manifestations (abdominal pain, vomiting, diarrhea) (more common in children)  
  - Rash (petechial, maculopapular, or diffuse erythema, usually affecting the trunk and extremities) (more common in children)  
  - Severe manifestations: toxic shock–like syndromes, renal failure, hepatic failure, coagulopathies, hemophagocytic lymphohistiocytosis  
  - Leukopenia and thrombocytopenia  
  - Anemia – occurs later than leukopenia or (thrombocytopenia  
  - Hyponatremia  
  - Elevated serum hepatic transaminase concentrations  
  - CSF abnormalities (pleocytosis with predominance of lymphocytes, increased total protein concentration)  
  - Morulae may be visualized during acute illness  |
| Anaplasmosis | 5–14 d | Systemic manifestations: see ehrlichiosis  
  - Gastrointestinal and CNS manifestations less frequent than in ehrlichiosis  
  - Rash in <10%  
  - Severe manifestations (see ehrlichiosis), less common than in ehrlichiosis  
  - Leukopenia and thrombocytopenia  
  - Hyponatremia  
  - Elevated serum hepatic transaminase concentrations  
  - Morulae may be visualized during acute illness  |

Continued
through blood product transfusion. (21)(22)(23)(24) Tick vectors in the United States for these organisms (Table 2) include the lone star tick (*Amblyomma americanum* (Fig 1), the blacklegged tick (*I scapularis*) (Fig 1), and the western blacklegged tick (*I pacificus*). (21)(22)(23)(24) The seasonality (21)(22)(23)(24) and geographic location (21)(22)(23)(24)(29) of infections with *Ehrlichia* species and *A phagocytophilum* are summarized in Table 2. In the United States, ehrlichiosis is most often reported from southeastern and south-central states (from the east coast to Texas) (Table 2, Fig 3), whereas anaplasmosis is most often reported from the northeastern and upper midwestern states (Table 2, Fig 4).

The incubation periods (21)(22)(23)(24) and clinical manifestations (20)(31)(32)(33) of, and the laboratory abnormalities (20)(33)(34) associated with, ehrlichiosis and anaplasmosis are summarized in Table 3. Many of the clinical manifestations of ehrlichiosis and anaplasmosis likely result from the body's systemic inflammatory response and not from direct effects of the bacteria. (24) The estimated case fatality rates among those with ehrlichiosis and anaplasmosis seeking medical care are 3% and less than 1%, respectively. (33)(35)(36)(37)(38) Although the incidence of ehrlichiosis due to *E chaffeensis* generally increases with increasing age, (29)(36)(39) the case fatality

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<tr>
<th>DISEASE</th>
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<th>LABORATORY ABNORMALITIES</th>
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<tr>
<td>RMSF</td>
<td>3–12 d</td>
<td>Early (1–4 d):</td>
<td>• Thrombocytopenia</td>
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<td></td>
<td></td>
<td>• Fever, chills, malaise</td>
<td>• Hyponatremia</td>
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<td></td>
<td></td>
<td>• Severe headache (less common in young children)</td>
<td>• Elevated liver transaminase concentrations</td>
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<td>• Myalgia</td>
<td>• Leukopenia</td>
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<td></td>
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<td>• Gastrointestinal symptoms (abdominal pain, nausea, vomiting, anorexia)</td>
<td>• Anemia</td>
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<td></td>
<td></td>
<td>• Edema, periorbital or on the back of hands</td>
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<td></td>
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<td>• Photophobia</td>
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<td>Late (5+ d):</td>
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<td>• Altered mental status, coma</td>
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<td>• Respiratory compromise (pulmonary edema, ARDS)</td>
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<td>• Necrosis (may require amputation)</td>
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<td>• Multorgan system damage (eg, CNS, renal)</td>
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<td>Rash:</td>
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<td>• Early (2–5 d after onset of symptoms): maculopapular rash on wrists and ankles, often spreading within hours, both proximally to the trunk and distally to the palms and soles (face is usually spared)</td>
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<td>• Late (day 6 or later after onset of symptoms): petechial rash</td>
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<td>Babesiosis</td>
<td>1–9 wk</td>
<td>Often asymptomatic or associated with only mild, nonspecific symptoms but can be a severe, potentially fatal disease</td>
<td>• Hemolytic anemia, elevated reticulocyte count</td>
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<td></td>
<td></td>
<td>• Fever common</td>
<td>• Thrombocytopenia</td>
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<tr>
<td></td>
<td></td>
<td>• Gradual onset of symptoms such as fatigue, malaise, and anorexia</td>
<td>• Proteinuria</td>
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<td>• Subsequently, influenza-like illness symptoms (fever, chills, arthralgia, myalgia, headache, nausea)</td>
<td>• Elevated concentrations of hepatic enzymes, creatinine, and blood urea nitrogen</td>
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<td></td>
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<td>• Other, less common symptoms: conjunctival injection, photophobia, pharyngitis, nonproductive cough, abdominal pain, vomiting, weight loss, emotional lability</td>
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<td></td>
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<td>• Possible respiratory distress, hypotension, mild hepatosplenomegaly, jaundice, dark urine, depression</td>
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<td>• Disseminated intravascular coagulation, renal failure, hemodynamic instability, respiratory distress, hepatic compromise, altered mental status, and death may occur with severe infection</td>
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ARDS=acute respiratory distress syndrome, CNS=central nervous system, CSF=cerebrospinal fluid, EM=erythema chronicum migrans.
**TABLE 4.** Tick-borne Diseases in Children in the United States: Diagnosis and Treatment

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
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| Lyme disease | Demonstration of diagnostic IgM or IgG antibodies in serum. A 2-tiered testing protocol is recommended: enzyme-linked immunosorbent assay or IFA assay should be performed first; if positive or equivocal, Western blot should follow | Early localized disease:  
- Doxycycline 4.4 mg/kg per day, PO, divided BID (maximum, 200 mg/d) for 10 d; OR  
- Amoxicillin 50 mg/kg per day, PO, divided TID (maximum, 1,500 mg/d) for 14 d; OR  
- Cefuroxime 50 mg/kg per day, PO, divided BID (maximum, 100 mg/d) for 14 d  
For patients intolerant to the above:  
- Azithromycin 10 mg/kg per day, PO, once daily for 7 d  
Extracutaneous disease:  
- Isolated facial palsy: doxycycline 4.4 mg/kg per day, PO, divided BID (maximum, 200 mg/d) for 14 d  
- Arthritis: an oral drug as for early localized disease, for 28 d  
- Persistent arthritis after first course of therapy: treat again using an oral agent as for first-episode arthritis for 28 d; OR ceftriaxone 50–75 mg/kg, IV, once daily (maximum, 2,000 mg/d) for 14–28 d  
- Atrioventricular heart block or carditis: an oral agent as for early localized disease, for 14 d (range, 14–21 d); OR ceftriaxone 50–75 mg/kg, IV, once daily (maximum, 2,000 mg/d) for 14–28 d (range, 14–21 d if hospitalized; can be changed to oral therapy once stabilized/discharged)  
- Meningitis: doxycycline 4.4 mg/kg per day, PO, divided into doses (maximum, 200 mg/d) for 14 d; OR ceftriaxone 50–75 mg/kg, IV, once daily (maximum, 2,000 mg/d) for 14 d |
| Ehrlichiosis | PCR assay to detect Ehrlichia DNA in whole blood  
- IFA assay: demonstration of a 4-fold rise in the Ehrlichia IgG-specific antibody titer in a pair of serum samplesa  
- Immunohistochemical staining of skin, tissue, or bone marrow specimens to visualize Ehrlichia species | Doxycycline (maximum, 100 mg per dose):  
- Children weighing <100 lb (<45.4 kg): 2.2 mg/kg per dose BID, PO or IV  
- Larger children and adults: 100 mg BID, PO or IV  
Duration of therapy: minimum, 5–7 days; therapy should be given until evidence of clinical improvement and at least 3 d after fever resolves |
| Anaplasmosis | PCR assay to detect Anaplasma phagocytophilum DNA in bloodb  
- IFA assay: demonstration of a 4-fold rise in the A phagocytophilum IgG-specific antibody titer in a pair of serum samplesc  
- Immunohistochemical staining of skin, tissue, or bone marrow specimens to visualize A phagocytophilum | Doxycycline (maximum, 100 mg per dose):  
- Children weighing less than 100 lb (45.4 kg): 2.2 mg/kg per dose BID, PO or IV  
- Larger children and adults: 100 mg BID, PO or IV  
Duration of therapy: 10–14 d |
| RMSF | IFA assay: demonstration of a 4-fold change (usually an increase) in IgG-specific antibody titers in paired serum samples (first sample obtained within first week of illness; second obtained 2–4 wk later)d  
- PCR assay for detection of rickettsial DNA in a biopsy specimen (eg, skin biopsy of a rash lesion)  
- Immunohistochemical staining of rickettsial organisms from biopsy specimen (eg, skin or other tissue) | Doxycycline (maximum, 100 mg per dose):  
- Children weighing <100 lb (<45.4 kg): 2.2 mg/kg per dose BID, PO or IV  
- Larger children and adults: 100 mg BID, PO or IV  
Duration of therapy: minimum, 5–7 d; therapy should be given until evidence of clinical improvement and at least 3 d after fever resolves |

*Continued*
rates are highest in both adults 70 years or older and children 10 years or younger. (29)(36) Ehrlichiosis in immunocompromised individuals is associated with an increased risk of death. (29)(36) But severe or fatal cases of ehrlichiosis have occurred in previously healthy children and young adults. (33)(40) Children with ehrlichiosis often are asymptomatic or only mildly symptomatic. (33)(35)(41) With ehrlichiosis, gastrointestinal manifestations and rash may be more common in children. (33)(41) More severe manifestations of ehrlichiosis include toxic shock– or septic shock–like syndromes, coagulopathies, renal failure, and hepatic failure. (42) Rarely, E. chaffeensis infection may result in hemophagocytic lymphohistiocytosis. (41)(43) Anaplasmosis is usually a self-limiting illness. (24) Gastrointestinal manifestations and central nervous system involvement occur less frequently in patients with anaplasmosis than in those with ehrlichiosis, (30)(44) and rash occurs in less than 10% of patients with anaplasmosis. (30)(44) Severe or life-threatening manifestations are less frequent with anaplasmosis than with ehrlichiosis. Factors associated with a more severe clinical course of ehrlichiosis or anaplasmosis include immunosuppression and delay in diagnosis or treatment. In cases of anaplasmosis, laboratory abnormalities are usually observed during the first week of clinical illness, and usually there are no CSF abnormalities. (38) The organisms (Ehrlichia species and A. phagocytophilum) multiply within cytoplasmic vacuoles of the target cells (monocytes or granulocytes), forming clusters of bacteria called morulae. (45) Such morulae may be visualized in the cytoplasm of these cells during the acute stage of illness and are highly suggestive of the diagnosis (but because examination of a blood smear is insensitive, finding morulae should not be used alone to rule in or rule out the diagnosis). Patients with anaplasmosis may have altered neutrophil function, which could result in neutrophils having ineffective microbial activity. (40)

Diagnostic assays for ehrlichiosis and anaplasmosis are summarized in Table 4. For both diseases, laboratory diagnosis can be accomplished in 3 different ways (21)(22)(23)(24): PCR assays to detect the organism’s DNA, IFA assays to detect antibodies against the organism, and immunohistochemical staining to visualize the organisms in tissue specimens.

Treatment of ehrlichiosis and anaplasmosis is summarized in Table 4 (21)(22)(23)(24). The first-line treatment for either disease is doxycycline. A clinical suspicion of ehrlichiosis or anaplasmosis is sufficient to initiate treatment.
Conversely, delaying initiation of treatment may result in severe illness or death.

**ROCKY MOUNTAIN SPOTTED FEVER**

A total of 37,376 infections with spotted fever group rickettsii (including *Rickettsia rickettsii*, *Rickettsia parkeri*, and *Rickettsia* species 364D) were reported in the United States from 2004 through 2016. (1) Table 2 summarizes characteristics of *R. rickettsii*, the causative organism of RMSF, first described in 1906. (46) *R. rickettsii*, a member of the family Rickettsiaceae, is an obligate intracellular, Gram-negative bacillus. (24)(47)(48) The organism primarily targets endothelial cells of the vascular system, inducing a diffuse vasculitis with resultant increased vascular permeability. (24)

The tick vector, (24)(47)(48) seasonality, (24)(47)(48) and geographic distribution of reported cases (49)(50)(51)(52) (53) are summarized in Table 2. *R. rickettsii* is transmitted by 3 different ticks (24)(47)(48): the American dog tick (*Dermacentor variabilis*) (Fig 1), the Rocky Mountain wood tick (*Dermacentor andersoni*), and the brown dog tick (*Rhipicephalus sanguineus*). RMSF and related rickettsioses have been reported throughout most of the continental United States but are more common in certain south/south central states (Table 2, Fig 5). (49)(50)(51)(52)(53)

The incubation period (54) and clinical manifestations (24)(47)(48)(55)(56)(57)(58)(59) of, and laboratory abnormalities associated with, RMSF are summarized in Table 3. Patients with severe disease often have a shorter incubation period (eg, ≤5 days) than those with milder disease. (60) Symptoms associated with RMSF evolve during the illness. (24)(47)(48) Early symptoms of RMSF (24)(47)(48) are observed during the first 1 to 4 days of illness. (55)(56) A rash usually appears a few days after the onset of symptoms, but most patients seek medical attention before the rash appears. (57)(58)(59) Most patients do not have the classic triad of a reported tick bite, fever, and rash at the time they initially present for medical attention. (55)(57) The rash associated with RMSF also evolves over time. (24)(47)(48) Classically, the rash begins as small, pink, blanching macules. Over the ensuing days, the rash usually becomes maculopapular, and there may be central petechiae. A petechial rash occurs relatively late (ie, at or after day 6

![Figure 3. Ehrlichiosis cases reported to the Centers for Disease Control and Prevention, 2016. (Reprinted with permission from Centers for Disease Control and Prevention. *Tickborne Diseases of the United States.* 5th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2018.)](http://pedsinreview.aappublications.org/)
of illness) and indicates an advanced infection. The absence of a rash does not preclude the diagnosis of RMSF (less than half of patients do not have a rash during the first 3 days of illness, and some patients do not ever develop a rash). (55)(57) Children younger than 15 years are more likely to have a rash and are more likely to develop a rash sooner than are older individuals. (55)(61)(62) Untreated RMSF can have severe clinical manifestations, and progression to severe disease can be rapid, even in previously healthy individuals. Late clinical manifestations of RMSF are more severe. (63)(64) Patients who are treated early in the infection may have only mild disease with relatively rapid resolution of symptoms. (24)(47)(48) The highest incidence of RMSF is in older individuals (60–69 years of age), although RMSF occurs in people of all ages. (49) Children younger than 10 years have the highest RMSF case fatality rate. (49) Significant long-term sequelae have been described in patients with severe RMSF, including cognitive impairment, blindness, and peripheral neuropathy. (61)(65)(66)(67)(68)(69) Laboratory values in patients with RMSF (57)(70)(71)(72) are often within normal limits or only slightly abnormal early in the infection. Laboratory abnormalities are more likely to be observed as the infection progresses. Damage to the vascular endothelium by *R. rickettsii* results in increased capillary permeability with widespread microhemorrhage and platelet consumption. (71) Hypovolemia leads to appropriate secretion of antidiuretic hormone with resultant hyponatremia. (72)

Diagnostic assays for RMSF are summarized in Table 4. (24)(47)(48) The diagnosis of RMSF must be a clinical diagnosis (based on the patient’s signs and symptoms) because treatment of a patient with suspected RMSF should be initiated as soon as the diagnosis is suspected; the diagnosis can be confirmed through laboratory testing. The gold standard for the laboratory diagnosis of RMSF is the IFA assay. Other diagnostic assays used to confirm the diagnosis of RMSF involve detection of the organism’s DNA (through a PCR assay) or visualization of the organism through immunohistochemical staining of a biopsy specimen (skin or other tissue). (24)

Treatment of RMSF is summarized in Table 4. (24)(47)(48) As soon as RMSF is suspected, therapy with...
doxycycline should be initiated. Initiation of treatment within the first few days of illness is associated with greater effectiveness (in terms of preventing mortality and decreasing morbidity) than if treatment does not begin until after the fifth day of illness. Doxycycline is the antibiotic of choice for all age groups for the treatment of RMSF.

BABESIOSIS

Between 2011 and 2016, 9,631 cases of babesiosis were reported in the United States. (73) In 2015 alone, there were 1,804 confirmed cases of babesiosis in the United States, primarily in New England and the mid-Atlantic area. (74) Table 2 summarizes characteristics of the causative organism (Babesia microti is the most common cause of babesiosis in the United States, but several other genetically distinct Babesia species exist [2]). Babesia species belong to the phylum Apicomplexa, which includes Plasmodium and other species. (75) The major cell target of these intracellular organisms is the red blood cell. (2)(73)(74)

Although Babesia infections can be transmitted through blood transfusion and congenitally, (73)(74) babesiosis is a primarily vector-borne disease. The vector for transmission of B microti is the blacklegged tick (I scapularis). (73)(74) Fig 1 shows the appearance of this tick. The white-footed mouse (Peromyscus leucopus) is the primary reservoir host for B microti in the United States. (74) Although not a reservoir host for B microti, the white-tailed deer (Odocoileus virginianus) can serve as a host for blood meals by the tick. (74) During the past several years, the increase in the deer population in some regions, including suburban areas, is likely related to the spread of the tick vector. (73) The seasonality of vector-borne transmission of B microti is summarized in Table 2 (73)(74). B microti infections have been acquired in the northeast as well as in the upper Midwest (76)(77)(78)(79) (Table 2, Fig 6). Occasionally, cases of babesiosis caused by other Babesia species have occurred in different parts of the United States, (80)(81) but the tick vectors and the reservoir hosts for these organisms are usually not known. (74)
The incubation period and clinical manifestations of, and laboratory abnormalities associated with, babesiosis are summarized in Table 3. \(2\)(73)(74) In patients with symptomatic babesiosis, clinical manifestations usually develop within weeks of exposure, although manifestations may not develop until months after initial infection. (73) Parasitemia may persist, both in treated and untreated patients, and, especially in immunocompromised individuals, may result in recrudescence weeks or months later. (73)(82)(83) Even asymptomatic individuals can have persistent (eg, for more than a year) parasitemia. (74) Although babesiosis is often asymptomatic or associated with mild and nonspecific symptoms, it can manifest as a severe, potentially fatal disease. (73)(74) An estimated 50% of children with babesiosis are asymptomatic or have only a mild viral-like illness. (84)(85)(86)(87) Severe presentations are more likely if the patient is elderly and/or immunocompromised (eg, asplenic). (73)(74)(88)(89)(90) The first report of a case of human babesiosis in 1957 was in an asplenic patient. (91) The clinical manifestations of babesiosis (2)(73)(74)(79)(80)(81)(85)(88)(89)(90)(92)(93)(94)(95) may resemble those of malaria. Although fever is common in patients with babesiosis, individuals at the extremes of age (eg, infants, the elderly) or those who are immunocompromised may be afebrile. (74) Organ failure and death may occur with severe infection. (73)(74)(88)(93) Hemolytic anemia and an elevated reticulocyte count are the most prominent laboratory abnormalities with babesiosis. (2)(73)(88)(93)(95)

Because the clinical manifestations of babesiosis are nonspecific, confirmation of the diagnosis requires laboratory testing. (2) The most reliable diagnosis of babesiosis is made in patients with the following 3 characteristics: 1) positive laboratory test results for Babesia, 2) residence in or travel to an area where Babesia is endemic, and 3) a viral infection-like illness. (2) Diagnostic assays for babesiosis are summarized in Table 4 (73)(74). The first method of diagnosis of babesiosis is the identification of intraerythrocytic Babesia parasites by microscopic examination of Giemsa- or Wright-stained peripheral blood smears (73)(74) in patients with acute, symptomatic infection; the “tetrad” (Maltese cross) form is pathognomonic. (73)(74) Other methods of diagnosis of babesiosis are PCR analysis (73)(74)(96) and
Treatment of babesiosis is summarized in Table 4. (73)(74) Treatment for asymptomatic individuals is not recommended, irrespective of laboratory assays positive for Babesia. (2) If an asymptomatic individual has 1 or more positive Babesia assays, the assays should be repeated, and treatment should be considered if parasitemia continues for more than 3 months. (2)(73) Treatment is recommended for active babesiosis (viral infection–like symptoms with either visualization of Babesia parasites on a blood smear or a positive PCR assay for Babesia). (2) Symptomatic individuals with positive Babesia serology assays but no parasites observed on blood smears and no positive PCR assays for Babesia should not be treated. (2) Treatment for patients with active babesiosis usually entails combination therapy for 7 to 10 days with either atovaquone plus azithromycin or clindamycin with quinine. (2)(73)(74)(75) A longer duration of therapy may be necessary in patients with severe disease or those who are persistently symptomatic until parasitemia resolves. (2) The regimen of choice for the treatment of mild babesiosis in children is oral atovaquone with azithromycin. (73)(74) Severe babesiosis (eg, with parasitemia greater than 10%, or those with severe hemolysis, or hepatic, renal, or pulmonary compromise) is usually treated with intravenous clindamycin with quinine. (2)(73)(74) Severely ill patients may require or benefit from other concomitant interventions, such as mechanical ventilation, dialysis, and exchange transfusion. (73)(74)(75) With mild-moderate babesiosis, clinical improvement within 48 hours and complete resolution of symptoms within 3 months of initiation of therapy should occur. (2) Patients with moderate to severe babesiosis should be monitored carefully during treatment for improvement in clinical and laboratory parameters and decrease in parasitemia. (2) For example, with severe babesiosis, daily or every-other-day monitoring of the hematocrit value and the percentage of parasitemia until the patient has improved and the parasitemia has decreased to less than 5% is recommended. (2) Persistent low-grade parasitemia may occur for months after initiation of antimicrobial therapy. (2) If blood smears or PCR assays for Babesia remain positive for 3 months or more after initial treatment, repeated treatment should be considered. (2) For patients with especially severe or persistent symptoms despite appropriate treatment, the possibility of co-infection with other organisms with the same tick vector (B burgdorferi and/or A phagocytophilum) should be considered. (2) Special treatment considerations for severely immunocompromised patients (74) include 1) a duration of therapy of at least 6 weeks, with negative blood smears for at least 2 weeks before treatment discontinuation, and 2) treatment with higher doses of oral azithromycin.

**PREVENTION**

Prevention of acquisition of tick-borne diseases entails primarily preventing tick bites and removing ticks as quickly as possible if attachment has occurred. (100) To prevent tick bites, the following practices can be instituted: use of an Environmental Protection Agency–registered insect repellent (http://www.epa.gov/insect-repellents), treating cats and dogs for ticks, checking for ticks daily, and showering or bathing soon after outdoor exposure. Environmental Protection Agency–registered insect repellents contain compounds such as DEET (N,N-diethyl-meta-toluamide). In addition to applying such an insect repellent to the skin, clothing and gear (eg, boots) can be treated with products containing permethrin. Treatment of household pets (dogs and cats) for ticks should be performed under the guidance of a veterinarian. When checking for ticks, it is especially important to check in the following areas: around the hairline and scalp, in and around the ears, behind the knees, between the legs, around the waist, and inside the umbilicus. Any tick found attached to the skin should be removed as soon as possible and, after removing the tick, the skin should be cleaned.

In general, antibiotic drug prophylaxis after a tick bite to prevent tick-borne diseases is not recommended. However, for one tick-borne disease, Lyme disease, antibiotic drug prophylaxis can be implemented if a tick bite has occurred. (100) A single dose of doxycycline for the prevention of Lyme disease could be administered to children (5): 200-mg dose (or 4.4 mg/kg for children weighing <100 lb [<45.4 kg]), if the following conditions are met (100): 1) the patient resides in or has traveled to a state highly endemic for Lyme disease (Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, Wisconsin); 2) the attached tick is an adult or nymph stage I scapularis tick; 3) the estimated duration of attachment is at least 36 hours; 4) prophylaxis can be initiated within 72 hours of tick removal; and 5) the patient has no contraindication to doxycycline.
Summary

- In general, the epidemiology of tick-borne diseases reflects the characteristics of the specific tick vector, including the tick’s known geographic distribution and seasonality. However, some tick-borne diseases are transmitted through other mechanisms (eg, congenital). Because of this, and in areas with high endemicity, there may be year-round incident “tick-borne” diseases.

- However, the epidemiology of tick-borne diseases in the United States is evolving, with new species being identified and the range of the tick vectors expanding. Although the most common clinical manifestations of and laboratory abnormalities associated with each tick-borne disease are known, not every infected individual has all such clinical manifestations or laboratory abnormalities with a given tick-borne disease, and the number and combination of clinical and laboratory findings experienced varies from one patient to the next. The possibility of concomitant tick-borne diseases (eg, *I. scapularis* ticks transmit Lyme disease, *B. miyamotoi* infections, anaplasmosis, and babesiosis) should be suspected if a patient’s clinical or laboratory features are more severe than usually observed with a given tick-borne disease. Because tick-borne diseases can be fatal, and because a delay in the initiation of treatment can be associated with a poorer prognosis, the diagnosis may be based on clinical suspicion alone (while confirmatory laboratory studies are pending). Diagnostic laboratory testing for tick-borne diseases is evolving toward assays with faster turnaround times and less dependence on acute and convalescent serology samples. Prevention of tick-borne diseases primarily involves avoiding exposure to ticks and tick bites, checking for attached ticks, and prompt removal of ticks if found attached to the skin. Lyme disease remains the only tick-borne disease for which antibiotic drug prophylaxis is recommended for certain patients known to have an attached tick.

References for this article are at http://pedsinreview.aappublications.org/content/40/8/381.
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This journal-based CME activity is available through Dec. 31, 2021, however, credit will be recorded in the year in which the learner completes the quiz.

1. A previously healthy 9-year-old girl presents to the office in July with an enlarging, red, nontender, and nonpruritic rash of her left thigh for the past 3 days. She has felt warm, and her mom noted an oral temperature of 100.8°F (38.2°C) today. She has also complained of being achy and having a headache. A tick was removed from the site of the rash 14 days ago. The family lives in rural Maine. She and her family traveled to Tennessee for 1 week 6 weeks ago. On examination she is afebrile and her vital signs are normal. There is an annular, 8-cm-diameter erythematous macular lesion on her left thigh without central clearing, eschar, or drainage. Her mother states that she is allergic to amoxicillin because she had a rash when she was an infant. Which of the following is most likely responsible for the transmission of her illness?
   A. Amblyomma americanum.
   B. Dermacentor andersoni.
   C. Dermacentor variabilis.
   D. Ixodes scapularis.
   E. Rhipicephalus sanguineus.

2. For the patient in question #1, which of the following is the most appropriate next step in management?
   A. Begin cephalexin therapy.
   B. Begin doxycycline therapy.
   C. Obtain a blood sample for Borrelia burgdorferi polymerase chain reaction (PCR).
   D. Obtain a serum sample for enzyme-linked immunosorbent assay B burgdorferi antibodies.
   E. Obtain a serum sample for Western blot B burgdorferi immunoglobulin (Ig) G and IgM antibodies.

3. A 17-year-old boy is seen in the office for follow-up of 2 months of fatigue that started in November. He also complains of headache 1 to 2 times per week. He has not had weight loss, arthritis, arthralgias, or rash. He states that he feels warm occasionally but when he checks his temperature it is normal. He removed a tick from his inguinal region 7 months ago and did not develop a rash at the site. He lives in Oklahoma with his family, and his only travel was a Caribbean cruise the previous summer. His mother is concerned that he has Lyme disease or some other tick-borne illness. His vital signs and physical examination findings are normal. A complete blood cell count, erythrocyte sedimentation rate, and hepatic transaminase levels are within normal limits. Which of the following is the most appropriate diagnostic test for tick-borne disease?
   A. Anaplasma phagocytophilum PCR on blood.
   B. A phagocytophilum IgG antibody on serum.
   C. B burgdorferi antigen assay on urine.
   D. B burgdorferi Western blot IgG and IgM on serum.
   E. No tick-borne disease testing is recommended.
4. A previously healthy 6-year-old girl presents to the office in June with a 3-day history of fever to a temperature of 103°F (39.4°C) and increasing malaise. She also complained of a headache the past day. Last night the parents noted a red rash on her arms and legs, which then spread to her trunk. The parents have not removed any ticks from the girl, but the mom removed a tick from her brother 2 weeks ago. The family lives on a farm in Arkansas and has 2 pet dogs. In the office her temperature is 102.3°F (39.1°C), heart rate is 124 beats/min, respiratory rate is 22 breaths/min, blood pressure is 98/60 mm Hg, and oxygen saturation is 97%. She is moderately ill appearing but not lethargic. Her examination is remarkable for a generalized erythematous, blanching macular exanthem that is more prominent on her hands, arms, feet, and legs and involves her palms and soles. There is no meningismus. A complete blood cell count, blood culture, comprehensive metabolic profile, urinalysis, and *Rickettsia rickettsii* IgG and IgM immunofluorescent antibody assay are pending. She is started on empirical intravenous ceftriaxone therapy. Which of the following is the most appropriate additional antimicrobial therapy?

A. Atovaquone and azithromycin.
B. Chloramphenicol.
C. Ciprofloxacin.
D. Doxycycline.
E. No additional antimicrobial therapy is needed pending laboratory results.

5. A 12-year-old boy presents to the office in August with a 2-day history of low-grade fever, headache, and generalized myalgia. Three days before the onset of fever he had anorexia and increasing fatigue. He lives in New York City. He went to upstate New York 3 weeks ago for a 3-day camping trip and removed a tick from behind his right ear. He never developed a rash at that site. Laboratory testing is remarkable for hemolytic anemia, an elevated reticulocyte count, mild thrombocytopenia, and elevated hepatic transaminase levels. Which of the following is most likely to confirm the diagnosis?

A. Acute and convalescent *R rickettsii* immunofluorescent antibody assay IgG serum antibody.
B. Blood for *B burgdorferi* PCR.
C. Blood for *Ehrlichia chaffeensis* PCR.
D. Manual review of Wright-stained peripheral blood smear.
E. Urine for *B burgdorferi* antigen.
Tickborne Diseases in Children in the United States
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Pediatrics in Review 2019;40;381
DOI: 10.1542/pir.2018-0304

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