Tick-borne Diseases

Jean Y. Rim, MD; and Stephen Eppes, MD

Ticks are blood-sucking arthropods which can act as vectors for numerous infections. The most common tick-borne diseases in the United States are Rocky Mountain spotted fever (RMSF), human monocytic ehrlichiosis (HME), and human granulocytic anaplasmosis (HGA), all caused

CME EDUCATIONAL OBJECTIVES

1. Recognize the epidemiology of common tick-borne diseases in the United States.
2. Develop an approach to diagnosis and management of various tick-borne infections.
3. Identify practical measures to prevent these diseases.

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by rickettsia; Lyme disease, caused by a spirochete; tularemia, caused by a gram-negative bacillus; and babesiosis, caused by an intra-erythrocytic protozoan.

The ticks that transmit these diseases belong to the family Ixodidae, also known as hard ticks (see Figure 1, page 392). These species tend to inhabit wooded or brushy areas populated by mammals. The geographic areas that are most endemic for these diseases support the tick life cycle and, in the case of the zoonoses, the animal reservoir of the infection. Tick-borne diseases are more common during spring and early summer, which parallels tick activity (see Figure 2, page 393). People at greater risk for tick-borne diseases include those with occupational or recreational exposure to ticks (eg, pet owners, animal handlers, and people who live near wooded areas). Most of these infections occur with significant frequency in the pediatric age range (see Figure 3, page 394), relating to outdoor activities enjoyed by children.

Some findings in tick-borne diseases are sufficiently distinctive that they can be clinically diagnosed; for example, erythema migrans is pathognomonic of Lyme disease. For most of these diseases, however, the differential diagnosis is broad, and a high index of suspicion
is required. If a tick-borne disease is entertained, a detailed history must be obtained and should include the following: history of tick exposure or bite, recreational (e.g., camping, hiking, fishing, hunting, gardening, walking dogs) or occupational exposures to tick-infested habitats, recent travel to areas endemic for specific tick-borne diseases, and similar illnesses in family members, neighbors, or pets. In many cases, the tick bite will be recalled. However, *Ixodes scapularis*, which transmits Lyme disease, HGA and babesiosis, is so small it is often unnoticed.

**ROCKY MOUNTAIN SPOTTED FEVER**

RMSF is the most common rickettsial disease in the United States. It is caused by the gram-negative, obligate intracellular bacterium *Rickettsia rickettsii*, which targets endothelial cells that line the small vessels of all major tissues and organs, thus causing a small-vessel vasculitis.

**Epidemiology**

In the United States, RMSF is most prevalent in the southeastern, south central and south Atlantic states. Based on passive surveillance, the estimated annual incidence of RMSF from 1997-2002 was 2.2 cases per 1 million people. About one half of reported cases of RMSF were from five states: North Carolina, South Carolina, Arkansas, Tennessee, and Oklahoma.¹

The disease is transmitted via a tick, which is both the vector and main reservoir. *Dermacentor variabilis* (American dog tick) is the main vector in the southeastern and south central states. *Dermacentor andersoni* (wood tick) is the prevalent vector in the western states. *Rhipicephalus sanguineus* (brown dog tick) is a vector found mainly in Arizona. The tick bite is painless and often goes unnoticed. A history of tick bite within 14 days of illness is reported in 60% of cases.²

**Clinical Features**

The incubation period of RMSF is 2 to 14 days, with a mean of 7 days. Early symptoms are nonspecific and include fever, myalgia, malaise, severe headache, anorexia, nausea, vomiting, and diarrhea. A recent retrospective study of 92 children with RMSF revealed that 98% had fever, 73% had nausea and/or vomiting, and 61% had headache.³ Patients also may have abdominal pain, which can be quite severe and thus lead to an incorrect diagnosis of acute surgical abdomen. Myalgia is pronounced, particularly involving the back and calves.

About 88% to 97% of patients with RMSF have a characteristic rash (see Table 1, page 395, and Figures 4a, 4b, page 396), which usually appears 3 to 5 days after onset of symptoms.⁴ It generally starts as an erythematous maculopapular rash and then usually evolves
into petechiae. The rash typically begins on the wrist and ankles, and then spreads both centrally and also to the palms and soles. Rash frequently occurs earlier in children than in adults.

Severe neurologic symptoms can include mental status changes, focal neurologic deficits, seizures, transient deafness, photophobia, and meningismus. Serious complications include renal failure, pulmonary edema, and gangrene of the digits, ears, and scrotum. These complications occur most frequently in patients who have had a severe case of RMSF, often as a result of delayed diagnosis and therapy.

Mortality is highest in children younger than 4 years (3% to 4%) and in adults older than 60 years (4% to 9%). Other factors associated with higher mortality include male gender, African-American race, chronic alcohol abuse, and glucose-6-phosphate dehydrogenase deficiency (G6PD).

If treated in a timely manner, the prognosis of RMSF is generally very good. However, in severe cases, long-term sequelae are possible. These include hearing loss, peripheral neuropathy, hemiparesis, gangrene, and bladder and bowel incontinence.

Differential Diagnosis

The differential diagnosis for RMSF includes enteroviral infection, infectious mononucleosis, parvovirus B19 infection with the papulopurpuric glove stocking presentation, leptospirosis, gastroenteritis, acute surgical abdomen, meningococcemia, human monocytic ehrlichiosis (HME), and human granulocytic anaplasmosis (HGA).

Diagnosis

The diagnosis of RMSF is primarily clinical and epidemiologic but can be supported by laboratory data. A complete blood count (CBC) and comprehensive metabolic panel should be obtained. White blood count (WBC) and hemoglobin are usually normal, although leukopenia and anemia can occur. An increased number of bands is generally observed. Thrombocytopenia, hyponatremia and mildly elevated hepatic transaminases may also develop. In the previously mentioned recent retrospective study of 92 children with RMSF, 59% had platelet counts less than 150,000/mm³ and 52% had serum sodium concentrations less than 135 mEq/dL.

Cerebrospinal fluid (CSF) analysis often shows a mildly elevated WBC of <100 cells/µL, with either a lymphocytic or polymorphonuclear predominance. The glucose level is usually normal, and in one-third of patients there is a mildly increased protein concentration (100 to 200 mg/dL).

The most specific and sensitive test for diagnosing RMSF is the indirect immunofluorescent antibody (IFA) assay, a serologic test in which antibodies bind to fixed antigens on a slide and are then detected by a fluorescein-labeled conjugate. The sensitivity of the IFA is largely dependent on the timing of the test. Generally, antibodies are detected by IFA as say 7 to 10 days after onset of symptoms, with a titer of 1:64 or greater considered diagnostic. The sensitivity is 94% to 100% after 14 days. This test should be done both at the time of presumptive diagnosis as well as 2 to 3 weeks later in order to observe an increase in antibody level. Negative results are common during the first 5 days of illness. IgM persists for 3 to 4 months, while IgG titers last for 7 to 8 months.

Some findings in tick-borne diseases are sufficiently distinctive that they can be clinically diagnosed; for example, erythema migrans is pathognomonic of Lyme disease.
For more rapid diagnosis, *R. rickettsii* can be identified in a skin biopsy using two different methods: amplification of DNA by polymerase chain reaction (PCR), and immunohistochemistry (IHC), which is staining of antigens with antibody in a formalin-fixed, paraffin-embedded skin biopsy. However, only select laboratories (public health, Centers of Disease Control and Prevention reference laboratories) generally perform these tests. The skin biopsy must be done prior to initiating antibiotics, as sensitivity for both PCR and IHC diminishes quickly once therapy is started.

**Treatment**

Early treatment (before day 5 of illness) is crucial, as delay in diagnosis and treatment leads to an increased risk of morbidity and mortality. In a retrospective study of 94 patients with RMSF, patients treated within 5 days of onset of illness had a significantly lower mortality rate (6.5%) than patients treated after the fifth day (22.9%) because there is no readily available laboratory test that can confirm the diagnosis within the first 5 days of illness, the decision to treat must be based on clinical judgment in an appropriate epidemiologic setting.

**Epidemiology**

In the United States, HME is most commonly found in the southeastern and south central states. Cases are most commonly reported in Missouri, Oklahoma, Tennessee, Arkansas, and Maryland. The average annual incidence of HME was 0.7 cases per 1 million people from 2001 to 2002. The vector for HME is *Amblyomma americanum*, and the reservoir is the white-tailed deer.

**Clinical Features**

The incubation period for HME is 5 to 10 days, with a mean of 7 days. The early signs and symptoms of HME include fevers, chills, headache, myalgias, and malaise. Patients may later develop nausea, vomiting, anorexia, and weight loss. Skin findings are not as common as in RMSF and occur in only one third of adult patients and in two thirds of children with HME. The rash may be macular, maculopapular, petechial, or diffuse erythema. It also occurs later in the illness, at a median of 5 days after onset of symptoms.
Neurologic symptoms can include mental status changes and meningismus. Complications can include seizures, coma, renal failure, respiratory failure, and congestive heart failure. In severely immunocompromised patients, such as patients with HIV or receiving immunosuppressant drugs, HME can cause a severe or even fatal infection.

**Diagnosis**

Common laboratory findings in HME include leukopenia, thrombocytopenia, and modest elevations in liver transaminase levels. CSF may show a mild pleocytosis (<100 cells/μL).

The gold standard for diagnostic testing is the IFA. A positive result is a four-fold increase or decrease in antibody titers between the acute and convalescent stages with a minimum peak titer of 1:64.

Unlike RMSF, if a clinician suspects HME, a peripheral blood smear may be helpful. A Wright-Giemsa stain of a peripheral smear may reveal monocytes containing morulae, which are intracytoplasmic inclusions of chirochiae. Up to 20% of patients with HME may have morulae visible on blood smear during the first week of infection.9

**Treatment**

The treatment of choice is doxycycline (see Table 2). Therapy should be continued for 3 days until after the patient is afebrile, which is usually a total of 7 to 10 days.

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**HUMAN GRANULOCYTIC ANAPLASMOSIS (HGA)**

HGA (formerly known as human granulocytic ehrlichiosis or HGE) is caused by the rickettsia Anaplasma phagocytophilum (see Figure 6, page 397), which targets granulocytes (neutrophils). Like HGE, HGA does not cause vasculitis.

**Epidemiology**

In the United States, HGA is most common in New England, New York State, and the upper midwest. The states with the highest incidence during 2001 to 2002 were Rhode Island, Minnesota, Connecticut, New York, and Maryland. The average annual incidence of HGA during that time period was 1.6 cases per 1 million people.1

The vector for HGA is *I scapularis* in New England and the north central states and *I pacificus* (western blacklegged tick) in northern California. The reservoirs are deer, elk, and wild rodents.

**Clinical Features**

The incubation period for HGA is 5 to 10 days. The early signs and symptoms include fever, headache, malaise, and myalgias. Less than 50% of patients have nausea, vomiting, diarrhea, cough, and arthralgias. Less than 10% of patients with HGA have a rash.

Neurologic symptoms can include mental status changes and meningismus, although meningoencephalitis is uncommon. Less common are facial weakness, brachial plexopathy, and demyelinating polyneuropathy have been reported. Complications can include seizures, rhabdomyolysis, renal failure, respiratory failure, and congestive heart failure.

**Laboratory Diagnosis**

Laboratory findings in HGA are similar to those in HME; although nonspecific, these can be a helpful clue to diagnosis. Leukopenia, neutropenia with a left shift, mild anemia, thrombocytopenia, and modest elevations of liver transaminase levels are found. CSF pleocytosis is rare in HGA.

The gold standard of diagnostic testing of HGA is the IFA serology. A positive result requires a four-fold rise in antibody titer; the minimum peak must be 1:80. As in HME, peripheral blood

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**TABLE 1.**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Presentation</th>
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</thead>
<tbody>
<tr>
<td>Rocky Mountain spotted fever</td>
<td>Fever; headache; myalgia; nausea/vomiting; WBC normal; hyponatremia</td>
</tr>
<tr>
<td>Human monocytic ehrlichiosis (HME)</td>
<td>Fever; headache; malaise; elevated transaminases; leukopenia</td>
</tr>
<tr>
<td>Human granulocytic anaplasmosis (HGA)</td>
<td>Fever; headache; myalgia; malaise; elevated transaminases; leukopenia</td>
</tr>
</tbody>
</table>

**TABLE 2.**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocky Mountain spotted fever (RMSF), human monocytic ehrlichiosis (HME), and human granulocytic anaplasmosis (HGA)</td>
<td>Doxycycline twice daily for 7 to 10 days</td>
</tr>
<tr>
<td></td>
<td>Younger than 12 years: 2.2 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Older than 12 years: 100 mg</td>
</tr>
</tbody>
</table>
smears may show morulae, except in HGA, they are in neutrophils. Additionally, it is more common in HGA to show morulae, because 20% to 80% of patients with HGA will have morulae detected during the first week of infection.

**Treatment**

Doxycycline is the drug of choice (see Table 2, page 395).

**LYME DISEASE**

The organisms that cause Lyme disease are spirochetes belonging to the genus *Borrelia*. In the United States, *Borrelia burgdorferi* is responsible for virtually all cases. In Europe, *B. garinii* and *B. afzelii* cause clinical manifestations that differ somewhat from North American Lyme disease.

**Epidemiology**

Lyme disease is the most common vector-borne disease in both Europe and North America; in the latter it is among the most common reportable diseases in both sexes and all age groups. In most regions of the United States, the vector is the deer tick, *I. scapularis*, which acquires the spirochete by feeding on the white-footed mouse, *Peromyscus leucopus*, the major reservoir of the bacteria. The coastal northeast, mid-Atlantic states, and parts of the upper Midwest are the areas most endemic for Lyme disease. *I. scapularis* can also transmit *A. phagocytophilum* (the agent of HGA) and *Babesia microti*, leading to co-infections.

**Clinical Features**

The main clinical manifestations of Lyme disease are presented in Table 3 (see page 397). After a minimum of 24 hours of tick attachment, the spirochete penetrates the dermis and causes the characteristic skin lesion, erythema migrans (EM), in the majority of patients. If lymphohematogenous dissemination occurs, infection may involve skin (multiple EM), central and peripheral nervous systems, heart, eyes, and joints. Even without specific antimicrobial therapy, early disease may resolve; however, there exists a potential for progression and significant morbidity. Months after the tick bite, late disease may occur, most often involving the joints; thus, Lyme arthritis is common in colder months, unlike most tick-borne disease manifestations.

The hallmark of early Lyme disease is EM, which is typically an annular erythematous lesion that enlarges over a period of days. This is the only manifestation of Lyme disease that is sufficiently distinctive to allow a clinical diagnosis without laboratory confirmation. Many variants of EM have also been described, including homogeneously erythematous lesions, those with a target-like appearance, and occasionally lesions with vesicles and pustules at the center that are likened to a spider bite. Early localized disease may be accompanied by mild constitutional symptoms.

Early disseminated disease often, but not always, presents with more pronounced constitutional symptoms and multiple EM is commonly seen (see Figure 7, page 398). In the early 1980s, 10% to 15% of untreated cases of early infection presented with neurologic involvement; more recent data indicate a lower frequency, possibly because of improved recognition and treatment of erythema migrans. The most frequent neurologic manifestation in the United States is cranial neuropathy; by far, the most common is peripheral facial nerve palsy or Bell's palsy. In Lyme-endemic areas,
25% to 50% of Bell’s palsy cases are caused by Lyme disease. Even though this is a peripheral nerve condition, it is associated with meningitis in many, if not most, affected children. The clinician who is evaluating a case of Bell’s palsy in a Lyme-endemic area, especially in the warmer months, should look for evidence of Lyme disease, including performing lumbar puncture if symptoms or physical findings suggest meningitis.

Lyme meningitis can be differentiated from viral meningitis (which also is most frequent in the summer time) based on history, physical findings, and cerebrospinal fluid (CSF) parameters. Lyme meningitis usually has a more indolent presentation (days to weeks of symptoms) with less fever, compared with viral meningitis. Cranial neuropathy and papilledema are much more common in Lyme disease, and erythema migrans is diagnostic. CSF pleocytosis in Lyme meningitis is typified by lymphocytes and monocytes (usually > 90%), whereas many cases of viral meningitis present with a polymorphonuclear predominance.

Cardiac involvement is most commonly manifested by conduction disturbances, particularly a fluctuating degree of heart block (see Figure 8, page 400). Occasionally, third degree heart block has been fatal. Clinicians evaluating patients with early disseminated Lyme disease should consider performing an EKG. Conversely, if conduction disturbances occur in previously healthy persons in the right epidemiologic setting, testing for Lyme disease should be done.

Lyme arthritis is usually oligoarticular and most commonly involves the knees. Various presentations have been described, but usually there is significant swelling (see Figure 9, page 400) and limitation of movement; pain and fever generally are not pronounced. Differentiation from other forms of arthritis is usually not difficult, based on clinical findings and strongly positive serologic results. If synovial fluid is examined, very high white blood cell counts (30,000 to 100,000/cu mm) are frequently observed; this may resemble findings of septic arthritis, but Gram’s stain and culture are negative.

In part because most patients are diagnosed and treated early in the course of infection, chronic neurologic Lyme disease is rare in the United States. Late neuroborreliosis may occur in the form of encephalomyelitis and/or peripheral neuropathy. Recent recommendations on diagnosis and treatment of these conditions have been published recently. Lyme encephalopathy, on the other hand, is imprecisely defined and some experts doubt this even exists as a distinct clinical entity. It is characterized mainly by subtle cognitive deficits, and there is no clear evidence that it responds to antibiotic therapy.

**Diagnosis**

There have been considerable efforts to develop laboratory tests for identifying infection with *B. burgdorferi*. For clinical purposes, these tests should be used only for patients who have compatible clinical findings in the right epidemiologic setting (ie, with a higher pre-test probability of infection). Classic EM lesions are diagnostic and require no laboratory confirmation. For all other presentations of Lyme disease, diagnosis may be facilitated by performing appropriate tests.

Serologic testing is the most useful modality in most cases. In the first few weeks after the tick bite, IgM antibody to *B. burgdorferi* becomes detectable, rapidly peaks, and then declines. After a month, most patients also develop IgG antibody, which may persist for months.

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**TABLE 3.**

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Timing after Tick Bite</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early localized</td>
<td>3 to 30 days</td>
<td>Erythema migrans (EM) – single variable constitutional symptoms: myalgia, arthralgia, fever, headache, fatigue</td>
</tr>
<tr>
<td>Early disseminated</td>
<td>3 to 12 weeks</td>
<td>EM — single or multiple constitutional symptoms: neck pain, meningitis, cranial neuritis (eg, facial palsy), radiculoneuritis, carditis (variable heart block), eye involvement</td>
</tr>
<tr>
<td>Late disease</td>
<td>&gt; 2 months</td>
<td>Arthritis</td>
</tr>
</tbody>
</table>

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*Figure 5. Ehrlichia chaffensis. Source: CDC.*

*Figure 6. Anaplasma phagocytophilum. Source: CDC.*
to years. In very early disease, therefore, there may be an incomplete antibody response. In early disseminated disease, including most patients with neurologic involvement, antibody tests (especially IgM) are usually positive. Patients with Lyme arthritis generally have very elevated antibody levels.

Clinicians ordering confirmatory testing should be aware that there are many approved, and some unapproved, tests that are available through commercial laboratories. For more than a decade, the two-test approach has been recommended for serologic diagnosis of Lyme disease. An enzyme-linked immunosorbent assay (ELISA or EIA), either measuring IgM and IgG together or individually, is the first step. The immunofluorescent antibody test has also been employed as a first test but is less commonly used today. These tests are sensitive, but not highly specific. A negative ELISA usually means the patient does not have Lyme disease. If the ELISA is positive or equivocal, it should be confirmed by the more specific Western blot test, which measures antibody to specific borrelial antigens, appearing as “bands” of either IgG or IgM antibody. Interpretive criteria for both are usually displayed on commercial laboratory reports. The use of western blot testing alone (ie, without ELISA) is discouraged, as incorrect interpretation can lead to over-diagnosis of Lyme disease.

Other tests are sometimes useful. Polymerase chain reaction (PCR) tests are commercially available. In patients with treatment-resistant Lyme arthritis, synovial fluid PCR results can be used to guide management decisions. The use of CSF PCR in children with neuroborreliosis is associated with low sensitivity and little clinical utility. The Lyme urinary antigen test has been discredited and is not recommended. Clinicians should also be aware that laboratories differ in their methodologies and reporting of results. Some laboratories have developed notoriety for high rates of positive results, including cultures and special stains for *B. burgdorferi*, which are not reproducible in other laboratories and are of questionable validity.

**Treatment**

Comprehensive guidelines for the treatment of Lyme disease, HGA, and babesiosis were recently published by the Infectious Diseases Society of America. A brief guide to therapy is presented in Table 4 (see page 399). Oral antibiotic therapy is recommended for patients with early localized disease, early disseminated disease (without CNS or significant cardiac involvement), and uncomplicated arthritis. Oral therapy is acceptable for cranial nerve palsy, provided there is no evidence of CNS involvement. Parenteral therapy is recommended for central nervous system disease, higher degrees of cardiac conduction abnormalities, and arthritis refractory to oral antibiotic therapy. For any presentation of Lyme disease, the minimum duration of treatment is 14 days. Up to 28 days of antibiotic therapy may be required for CNS infection, depending on clinical response, and 28 days is recommended for Lyme arthritis.

When promptly diagnosed and treated, most children with Lyme disease recover completely. Delays in effective therapy, however, have been associated with protracted symptoms. Fatal cases,
mainly involving cardiac disease, have been reported rarely. Chronic, incurable infection, although described in lay media and on the internet, has never been shown to occur. Post-Lyme disease syndrome, a vaguely defined condition following Lyme disease, has been seen mainly in adults and appears to be unusual in children. Case reports have been published regarding neurocognitive abnormalities in children who have had Lyme disease; however, larger studies have described very favorable neurocognitive outcomes.

TULAREMIA

Tularemia, caused by the gram-negative coccobacillus Francisella tularensis, is a zoonotic disease that is associated primarily with tick bites and infected animals, especially rabbits. The organism is highly virulent; only a few organisms are required to produce disease.

Epidemiology

The disease was more common early in the 20th century; the peak incidence in the United States was in 1939 when 2,300 cases were reported. It has become less common, in part because wild rabbits are no longer sold in markets. During the decade of 1990-2000, 1,368 cases were reported to the CDC, of which most occurred in males, with children and the elderly having the highest rates. Human disease has been reported from most areas of the United States, but the highest concentration of cases is in the states of Arkansas, Missouri, and Oklahoma.

Natural infection in humans can occur by a variety of mechanisms and can result in several different clinical presentations. Most cases now are transmitted by arthropods, including ticks (D. variabilis, D. andersoni, and A. americanum) and the deer fly (Chrysops discalis).

Direct contact with infected animals (especially rabbits and hares), consumption of the flesh of such animals, ingestion of contaminated food or water, and inhalation of aerosolized organisms are other routes of infection. Further interest has been focused on F. tularensis recently as a potential agent of bioterrorism.

Clinical Features

All forms of tularemia present as an acute febrile illness, often with associated chills, headache, malaise, and anorexia. Characteristically, fever lasts for several days, remits for a short period, and then recurs along with other symptoms. Among survivors, the mean duration of fever is about 1 month, and chronic debility and weight loss can go on for months. Based on the route of infection, several different clinical presentations may occur. Ulceroglandular disease (see Figure 10, page 401) is most

TABLE 4.

Antibiotics Useful for Treating Lyme Disease, Based on Clinical Situation.
(See text for details and for duration of treatment.)

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Usual Treatment*</th>
<th>Alternative Agents*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Localized Lyme Disease</td>
<td>Doxycycline by mouth, amoxicillin, cefuroxime axetil</td>
<td>Macrolides (erythromycin, larithromycin, azithromycin)</td>
</tr>
<tr>
<td>Early Disseminated Lyme Disease without CNS involvement and with no more than first-degree heart block</td>
<td>Doxycycline by mouth, amoxicillin, cefuroxime axetil</td>
<td>Macrolides</td>
</tr>
<tr>
<td>Early Disseminated Lyme Disease with CNS involvement, or symptomatic carditis, or PR interval &gt; 0.3 sec., or second- or third- degree heart block</td>
<td>Intravenous ceftriaxone</td>
<td>Intravenous penicillin G; Doxycycline (intravenously or by mouth)</td>
</tr>
<tr>
<td>Late Lyme Disease with arthritis</td>
<td>Doxycycline by mouth, amoxicillin, cefuroxime axetil</td>
<td>Intravenous ceftriaxone;** intravenous penicillin GV**</td>
</tr>
<tr>
<td>Late Lyme Disease with CNS involvement</td>
<td>Intravenous ceftriaxone</td>
<td>Intravenous penicillin G; Doxycycline (intravenously or by mouth)</td>
</tr>
</tbody>
</table>

*Dosage: Doxycycline: (100 mg twice daily (pediatric: 2 to 4 mg/kg/day for 2 days)
Amoxicillin: 500 mg three times daily (pediatric: 50 mg/kg/day for 3 days)
Cefuroxime axetil: 500 mg twice daily (pediatric: 20 to 30 mg/kg/day for 2 days)
Erythromycin: 250 mg 4 times daily (pediatric: no data for Lyme disease)
Clarithromycin: 500 mg twice daily (pediatric: no data for Lyme disease)
Azithromycin: 500 mg on day 1 and 250 mg 4 times daily (pediatric: no data for Lyme disease)
Ceftriaxone: 2 grams 4 times daily (pediatric: 100 mg/kg/day)
Penicillin G: 20 million units/day with dosing every 4 to 6 hours (pediatric: 200,000 to 400,000 units/kg/day with dosing every 4 to 6 hours)
**For severe or refractory cases
common: at the site of inoculation (most commonly from a tick bite), a red, tender papule develops, eventually forming an eschar. As the bacteria spread to regional lymph nodes, tender lymphadenitis results. Bacteremia may also occur at this stage and result in infection of multiple organs. Glandular tularemia refers to the presentation with fever and regional lymphadenopathy but without an evident site of inoculation. Oculoglandular disease occurs when organisms gain entry via the conjunctivae and is characterized by painful conjunctivitis, often with corneal ulceration and preauricular lymphadenopathy (a form of Parinaud’s syndrome). Pharyngeal tularemia results from ingestion or inhalation of infected material and presents with severe sore throat and exudative tonsillitis. Pneumonic tularemia results from inhalation of organisms and is associated with occupational exposure (eg, sheep shearers, farmers, and laboratory workers) and aerosolization of vegetable matter (as in a recent outbreak on Martha’s Vineyard). Pulmonary involvement is often severe and unresponsive to conventional antibiotic therapy for pneumonia. Clinicians who see cases of pneumonic tularemia should consider the possibility of a bioterrorism event and be vigilant concerning proper notification of public health authorities. Typhoidal (septicemic) tularemia is not accompanied by focal disease at the portal of entry; patients are often severely ill and may develop shock, renal dysfunction, and meningitis.

In up to 35% of cases of tularemia, secondary skin rashes occur. These may be maculopapular, vesiculopapular, erythema multiforme, or erythema nodosum. Lymphadenopathy can last weeks to months, and not infrequently suppurates and drains.

**Diagnosis**

Results of routine laboratory testing are nonspecific. The diagnosis of tularemia can only be made if the clinician suspects it. Because tularemia may cause severe illness, empiric treatment should be started while awaiting results of confirmatory testing, if clinical suspicion is high.

Cultures of blood and other specimens may grow the organism if processed on supportive media. However, the laboratory should always be informed of the potential biohazard; fatal tularemia is well reported among exposed laboratory workers. A PCR assay has been developed and is potentially rapid as well as accurate. Rapid diagnosis has become a more urgent matter as a result of the potential for *F. tularensis* to be used as an agent of bioterrorism. Direct fluorescent antibody testing and urine antigen detection have been advocated but are not in widespread clinical use.

The usual means to confirm infection is serologic testing. Unfortunately, antibodies may not be detectable in the first week of illness. Classically, a four-fold or greater rise in antibody as determined by an agglutination technique has been considered diagnostic. Many commercial laboratories offer ELISA tests which are reasonably sensitive and specific.
Treatment

Streptomycin traditionally has been the drug of first choice, but gentamicin is an acceptable alternative. Tetracyclines are bacteriostatic against the organism and, although they may appear effective, relapses may occur after treatment. Experience with ciprofloxacin and other fluoroquinolones for childhood tularemia is promising, these agents offer the advantage of oral dosing.

In the pre-antibiotic era, up to one third of tularemia cases had a fatal outcome. Today the fatality rates is considerably lower, but severe disease and prolonged symptoms may still occur, as noted above.

BABESIOSIS

Babesia species are intraerythrocytic protozoa (see Figure 11, page 402). The ring forms actually resemble those of Plasmodium species. However, the piroplasm undergoes asexual budding into merozoites in an asynchronous fashion so, unlike malaria, massive hemolysis rarely occurs. The species associated with human disease in the United States is Babesia microti.

Epidemiology

The main reservoir for B. microti is the white-footed mouse, and the primary vector is I. scapularis. In both respects, this is similar to the epidemiology of B. burgdorferi (Lyme disease). I. scapularis also transmits A. phagocytophilum, so it is not surprising that human coinfections with combinations of these three organisms can result from a single tick bite. The incidence of babesiosis is highest in southern coastal New England (especially the coastal islands) and eastern Long Island and Shelter Island, NY. Parts of New Jersey, Minnesota, and Wisconsin are also endemic. Deer are an important host for the tick; an increase in deer populations in certain geographic regions, including suburban locations, has contributed to the increase in human cases of babesiosis, as has occurred with Lyme disease over the past 30 years. B. microti has also been transmitted by blood transfusions. Reported cases of babesiosis are more common in adults than in children, possibly because the disease tends to be more severe in older adults.

Clinical Features

Many infections are asymptomatic or mild. When symptoms occur, they are reminiscent of malaria, as they are related to both the immune response to the organism and to hemolysis. Fever, chills, achiness, malaise, nausea, and vomiting are common. Hemolysis is usually mild, but both pallor and jaundice may be observed. Examination may reveal hepatomegaly and/or splenomegaly. Laboratory findings include anemia, often with reticulocytosis, thrombocytopenia, elevation of creatinine and blood urea nitrogen, and abnormal liver function tests. More severe disease occurs in patients who are immunocompromised, especially those who are asplenic. Complications may include respiratory failure, disseminated intravascular coagulation, heart failure, renal failure and coma.

Diagnosis

Babesiosis occurs only in people who reside in, or have visited, endemic areas. Therefore, epidemiologic factors weigh considerably in diagnosis. Tests for B. microti should not be ordered for non-specific febrile illnesses when there is no epidemiologic plausibility.

In most cases, the diagnosis is made by observing the organism in Giemsa- or Wright-stained blood smears. Multiple thick smears may need to be examined if there is low level parasitemia. PCR assays for B. microti DNA appear to be more sensitive than microscopic detection. Serologic testing has tradi-
tionally been done using IFA; a titer of 1:64 is diagnostic of infection, and either a single titer of 1:256 or a 4-fold or greater rise indicates acute infection. EIA is also available and correlates well with both IFA and PCR.26

Many experts also recommend testing for Lyme disease when babesiosis is diagnosed, because of the likelihood of coinfection.

**Treatment**

All patients with acute babesiosis should receive antimicrobial therapy, because of the risk of severe illness. Two regimens are efficacious. Intravenous clindamycin (20 to 40 mg/kg/day, up to 600 mg three times per day) plus quinine (25 mg/kg/day, up to 650 mg three times per day) is recommended for severe illness. The regimen of atovaquone (40 mg/kg/day, up to 750 mg twice per day) plus azithromycin (12 mg/kg/day, up to 600 mg daily) is better tolerated. Treatment is administered for 7 to 10 days. In severe disease, partial or complete exchange transfusion is indicated.

**PREVENTION OF TICK-BORNE INFECTIONS**

Clinicians should be aware of the ticks and tick-borne diseases prevalent in the area in which they practice. The cornerstones of prevention are 1) avoidance of tick-infested areas; 2) measures to reduce tick populations in the environment; 3) personal protective measures; and 4) removing attached ticks as quickly and completely as possible.

For Lyme disease, it has been shown that children are most likely to acquire infection close to their own home.28 Maintaining the property edge and reducing leaf litter can reduce the opportunity for *I. scapularis* to populate the home environment. Keeping pets free of ticks decreases the likelihood of exposure to ticks that feed on those species. Chemically treating properties to kill or repel ticks has been recommended in the past but may be expensive and/or impractical.

Recommendations for personal protection when outdoors in tick infested areas include wearing long-sleeved shirts, long pants tucked into socks, and hats. These measures have never become popular, especially with children and adolescents, and have never been proven to be very effective. Treating clothing, socks, and shoes with a tick repellent such as DEET (N,N-diethyl-3-methyl-benzamide) may be somewhat more effective. DEET may also be applied to skin and, although there have been reports of neurotoxicity in children treated with DEET, the risk is low when products are applied properly.27

Frequent inspection of children for ticks helps to identify early tick attachment. Most infections can be prevented effectively if the tick is removed quickly. For example, for *B. burgdorferi* to cause human infection, the tick must be attached for 24 to 48 hours. The tick should be grasped with tweezers at the mouth parts, as close to the skin as possible, and pulled directly out without twisting. If fingers are used, a tissue should be wrapped around the tick before grasping and hands washed afterward.

The use of chemoprophylaxis (antibiotics) for tick bites is controversial. This approach has been best studied in the setting of Lyme disease. Current guidelines do not recommend routine use of chemoprophylaxis. Only one study demonstrated clear benefit; a single 200 mg dose of doxycycline given to adults, compared with placebo, significantly reduced the frequency of EM.29 Recent guidelines10 suggest that this strategy could be used in children > 8 years if all of the following conditions apply: a) tick is reliably identified as *I. scapularis* and has been estimated to be attached > 36 hours; b) doxycycline can be administered within 72 hours; c) local rate of infection of deer ticks with *B. burgdorferi* is > 20%; and d) doxycycline is not contraindicated. Amoxicillin is not recommended in this setting. Clinicians should advise people with known deer tick attachments to watch the area for development of EM for 30 days and to report any skin lesions or constitutional symptoms should they occur. The majority of patients with early localized Lyme disease respond rapidly when treated with appropriate antibiotics.

**REFERENCES**


7. Clemens ML, Dmuser JS, Fiest P, Wiseman CL, Snyder MJ, Levine MM. Serodiagnosis of Rocky Mountain spotted fever: comparison of IgM and