Primary Care Reports
The Practical CME Journal for Primary Care and Family Physicians
Volume 20, Number 6 / June 2014
www.ahcmedia.com

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**Statement of Financial Disclosure**

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Kim (author), Dr. Gatewood (author), Dr. Quan (peer reviewer), Dr. Wise (editor), Ms. Coplin (executive editor), and Ms. Kimball (managing editor) report no financial relationships relevant to this field of study.

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# Tick-borne Illness: Evaluation and Management

*This article originally appeared in the Feb. 9 and Feb. 23, 2014 issues of* Emergency Medicine Reports.

Ticks are obligate, blood-feeding arthropods that are closely related to mites, spiders, and scorpions. There are 865 species of ticks worldwide, approximately 80 of which are endemic to the United States. The majority (approximately 700 species) belong to the family *Ixodidae*, also known as "hard ticks." Roughly 180 belong to the family *Argasidae* ("soft ticks"), and one species, only found in Africa, belongs to the family *Nuttalliellidae*.[1,2]

Ticks are an important vector for arthropod-borne disease throughout the world. Their disease burden ranges from local inflammation to fulminant systemic infection by transmitting viruses, bacteria, and/or parasites as they feed on the unsuspecting person. As one tick may transmit multiple microbial pathogens, there is the potential for significant morbidity and mortality related to a single exposure. It is now widely known that ticks are the source of multiple diseases throughout the United States.[2]

The life cycle of a tick begins when a larva hatches from the egg. The larva, once large enough, will attach to a host to feed. It then molts into a nymph. The nymph attaches, feeds, drops, and molts into an adult. The adult female tick will feed on its host, engorge, produce 1000-18,000 eggs, and die. The transmission of diseases occurs during the days when the tick is attached to its host to feed.[2]

Simple techniques to prevent insect bites, including wearing long-sleeved clothing and using insect repellent, can help reduce the likelihood of tick attachment. Patients who live in locations endemic to ticks can be counseled to examine their skin for ticks following outdoor activities in grassy or forested areas. If found, the tick may be removed by using thin-tipped tweezers to grasp the tick as close as possible to the skin and pulling with steady pressure without using any twisting motion. The tick should be saved for future reference.[2]

Of the approximately 80 species of ticks in the United States, roughly 12 species are known to be of health or veterinary significance.[2] The majority of these are hard ticks that belong to the family *Ixodidae*. This article will discuss the major tick-borne illnesses seen in the United States. Diseases endemic to other countries, including Crimean-Congo hemorrhagic fever and Helvetica spotted fever, will not be discussed in this review.

## *Ixodes Scapularis*

*Ixodes scapularis* (formerly also referred to as *Ixodes dammini*),[3] more commonly referred to as the deer tick or the blacklegged tick, is one of the most common species of ticks known to transmit disease in the United States, where it is widely distributed in the northeastern, midwestern, and southern portions.[4]

The distribution of *I. scapularis* is closely related to the abundance of its primary host, the white-tailed deer. The population growth of the white-tailed deer in the northeastern United States in the 20th century allowed populations of deer

## Executive Summary

- Lyme disease is the most common vector disease. It often presents with erythema chronicum migrans in its earliest and most treatable stage. Systemic involvement, including carditis, neurological, and ocular, can occur soon after the tick bite. Later, arthritis and neuropsychiatric changes can occur.
- Patients with erythema chronicum migrans should be treated empirically without serologic testing. Patients who present within 72 hours of a tick bite should be treated prophylactically.
- Babesiosis is a tick-related illness seen more commonly in the Midwest. It causes hemolysis and the classic finding of "Maltese cross" formations within the red cells.
- Anaplasmosis is a bacterium that affects granulocytes and causes fever, chills, and altered mental status.
- Rocky Mountain spotted fever is most common in the southeastern United States despite its name. It presents with headache, fever, myalgias, and a vasculitic rash that may involve the palms and soles.
- Tularemia is often acquired by hunters who process infected animals. The classic finding in tularemia is fever without tachycardia.
- Tick paralysis or tick toxicosis presents with ascending paralysis and is cured with the removal of the tick.
- Ehrlichliosis is seen most commonly in immunosuppressed patients (HIV) and presents with nausea, vomiting, and abdominal pain. It can progress to ARDS, renal failure, carditis, or DIC.

ticks to thrive.[3] An unintended consequence of this is the current high incidence of diseases carried by this tick.

Blacklegged ticks are characterized by being dark brown to black in color. They have no white markings. The adult forms exhibit sexual dimorphism, with female ticks having an orange-red area on the caudal aspect of their bodies. The adult male tick feeds sparingly, and is a less significant contributor to disease. Due to their sheer number, small size, and coincident increased outdoor activity of people in the early summer, the blacklegged tick nymph carries the greatest disease burden.[3]

## Lyme Disease

*A 37-year-old man presents after a syncopal event. He felt palpitations prior to loss of consciousness for about 20 seconds. He was slightly confused after waking up. He relates having flu-like symptoms 2 weeks prior to his presentation. The patient last went on a hike 1 month ago. He is bradycardic, and the exam shows an erythematous rash on his posterior neck extending into his scalp. He has a third-degree heart block on EKG.*

The most widely recognized tick-borne infection is Lyme disease. In the 1970s, following a small epidemic of a mysterious inflammatory arthritis that occurred in children residing in and around Lyme, Connecticut, an association between Lyme disease and the spirochete *Borrelia burgdorferi* was made.

**Epidemiology.** Lyme disease is the most commonly reported vector-borne disease in the United States, with 248,074 cases reported to the CDC between 1992 and 2006. It is also reported in Asian and European countries. Its incidence peaks in the midsummer months. The primary vector is *I. scapularis*, especially in the eastern United States. However, *Ixodes pacificus* is the principal vector for Lyme disease in the western part of the country. Its incidence has steadily increased, with 9908 cases in 1992 and 19,931 cases in 2006. The majority of cases are reported from the northeastern and north central states. It is reported more frequently in children between the ages of 5 years and 14 years of age, with no significant difference between genders.[6]

**Clinical Presentation.** The presentation for Lyme disease is variable during the course of illness. The dermatologic, neurologic, musculoskeletal, and cardiac systems may be involved. Its presentation is broadly categorized into three different stages: early localized, early disseminated, and late disseminated.

*Early Localized*. The earliest stage of Lyme disease in all populations is manifested by the characteristic skin lesion known as erythema chronicum migrans (ECM). ECM usually presents as a solitary lesion that occurs at the site of the tick bite 3-30 days following the bite. Most patients do not remember a tick bite, so the absence of a tick bite on the history does not exclude Lyme disease. ECM is characterized as a non-tender, erythematous, annular lesion that expands centrifugally, with partial central clearing that is greater than 5 cm at its widest point. This lesion should be differentiated from a lesion that can occur due to a localized allergic reaction near the site of the bite. The central aspect of this lesion may become vesicular or necrotic. It is important to note that a minority (about 20%) of infected patients may not exhibit ECM.[7]

ECM does not always present classically. The lesion may be pruritic, tender, multiple in number, or without central clearing. Constitutional symptoms, including fatigue, arthralgia, myalgia, headaches, meningeal signs, fevers, and chills, may be present.[8]

*Early Disseminated*. Following the initial localized infection, the *Borrelia* spirochetes spread hematogenously throughout the body, leading to systemic, cardiac, neurological, ocular, and dermatological findings. Patients may present in this stage of Lyme disease without a history of localized ECM. In the weeks to months following the bite, patients exhibit severe nonspecific symptoms that resemble many other infectious, rheumatologic, or malignant diseases. Symptoms include fatigue, headache, myalgia, meningismus, fever, chills,

**Table 1:** Summary of Tick-borne Diseases Endemic to the United States

| Disease/ Organism | Vector | Presentation | Laboratory Findings | Diagnosis | Treatment |
|---|---|---|---|---|---|
| Lyme Disease<br>*Borrelia burgdorferi* | *Ixodes scapularis*<br>*Ixodes pacificus* | **Early localized:**<br>Erythema chronicum migrans, constitutional symptoms<br>**Early disseminated:**<br>Multiple ECM, constitutional symptoms, neurological symptoms, carditis<br>**Late disseminated:**<br>Arthritis, encephalopathy, dermatological changes | Blood:<br>• Nonspecific findings<br>CSF:<br>• Consistent with aseptic meningitis | Serology:<br>• ELISA<br>• Western blot<br>• Can be performed on CSF<br>• Urine antigen<br>• PCR<br>• Immunofluorescence | Nonpregnant adults, children > 8 years old:<br>• Doxycycline<br>• Amoxicillin<br>• Cefuroxime axetil<br>Pregnant adults, children < 8 years old:<br>• Amoxicillin<br>• Cefuroxime axetil<br>Any neurologic or cardiac involvement:<br>• Ceftriaxone<br>• Cefotaxime<br>• Penicillin G |
| Anaplasmosis<br>*Anaplasma phagocytophilum* | *Ixodes scapularis*<br>*Ixodes pacificus* | Constitutional symptoms, altered mental status. Immunocompromised patients may have multi-organ dysfunction, and meningoencephalitis | Blood:<br>Leukopenia, lymphopenia, transaminitis, elevated alkaline phosphatase | Blood smear:<br>• Intracellular morula<br>• Immunofluorescence<br>• Culture<br>• PCR | • Doxycycline<br>• Rifampin may be considered in pregnant adults and children |
| Babesiosis<br>*Babesia microti*<br>*Babesia ducani*<br>*Babesia divergens* | *Ixodes scapularis* | Constitutional symptoms, jaundice, abdominal pain, anorexia, nausea, diarrhea, photophobia, neurovegetative symptoms | Blood:<br>• Hemolytic anemia<br>• Thrombocytopenia<br>Urine:<br>• Hemoglobinuria<br>• Proteinuria | Blood smear:<br>• Maltese cross<br>• Immunofluorescence<br>• PCR | • Atovaquone and azithromycin<br>• Clindamycin and quinine for severe disease |
| Tick-borne Encephalitis<br>Powassan virus<br>Deer tick virus | *Ixodes* species | Meningoencephalitis | CSF:<br>Similar to aseptic meningitis | CSF:<br>• Detection of viral genome<br>• Positive viral serology | • Supportive care<br>• Empiric treatment for other causes of meningoencephalitis |
| Rocky Mountain Spotted Fever<br>*Rickettsia rickettsii* | *Dermacentor variabilis*<br>*Dermacentor andersoni*<br>*Rhipicephalus sanguineus* | Headache, fever, myalgia, vasculitic rash involving palms/soles that migrates to the trunk | Blood:<br>• Anemia, thrombocytopenia<br>• Elevated LFTs<br>• Azotemia<br>• Hyponatremia<br>CSF:<br>Similar to aseptic meningitis | Clinical diagnosis | • Doxycycline for all patients<br>• Chloramphenicol can be considered for pregnant adults, children, and those with tetracycline allergy |
| Tularemia<br>*Francisella tularensis* | *Dermacentor variabilis*<br>*Dermacentor andersoni*<br>*Amblyomma americanum* | • Constitutional symptoms-high fever without tachycardia.<br>• Non-healing ulcer, lymphadenopathy, pneumonia, meningitis, ocular symptoms | Blood:<br>Generally minimal changes on CBC, or LFTs | Serology<br>Immunofluorescence<br>PCR<br>Immunohistochemistry<br>Latex/tube agglutination<br>Culture | • Streptomycin is gold standard<br>• Gentamicin is more readily available<br>• Doxycycline for mild/moderate disease<br>• Chloramphenicol and streptomycin for meningitis<br>• Ciprofloxacin or doxycycline for post exposure prophylaxis |

migratory polyarthralgia, and malaise. ECM or other rashes may occur at multiple sites. Hepatosplenomegaly or lymphadenopathy may be present. Fatigue and lethargy are the symptoms that are most constant in this stage of disease. Other manifestations may be fleeting. Ocular involvement may occur with anterior uveitis or conjunctivitis.[7] Other cutaneous manifestations, including lymphocytoma, can occur, but are more frequently observed in Europe.

*Early Neurological Involvement.* Acute neurological involvement often occurs during this stage. This includes lymphocytic meningitis, cranial neuropathies (especially of the seventh

**Table 1:** Summary of Tick-borne Diseases Endemic to the United States *(continued)*

| Disease/ Organism | Vector | Presentation | Laboratory Findings | Diagnosis | Treatment |
|---|---|---|---|---|---|
| Colorado Tick Fever<br>Colorado tick fever virus | *Dermacentor andersoni* | • Constitutional symptoms.<br>• Rarely, meningo-encephalitis, carditis, orchitis, pneumonia | Blood:<br>• Leukopenia, thrombocytopenia | • PCR in the 1st week<br>• Serology between weeks 2 and 4 | Supportive care |
| Tick Paralysis<br>Toxin-induced | *Dermacentor variabilis*<br>*Dermacentor andersoni* | • Restlessness, irritability, lethargy followed by ataxia and ascending, flaccid paralysis | | Identification of tick<br>Nerve conduction studies:<br>• Demyelination<br>• Axonal loss | Removal of tick |
| Ehrlichiosis<br>*Ehrlichia chaffeensis*<br>*Ehrlichia ewingii* | *Amblyomma americanum*<br>*Dermacentor variabilis* | • Constitutional symptoms, nausea, vomiting, abdominal pain, rash in HIV patients and children.<br>• May progress to ARDS, ARF, carditis, or DIC | Blood:<br>• Pancytopenia<br>• Elevated LFTs<br>• Azotemia<br>• Elevated LDH, amylase | Blood smear:<br>• Intracellular morula<br>PCR<br>Immunofluorescence<br>Culture | • Doxycycline is first line for all patients<br>• Rifampin may be considered in pregnant adults, children < 8 years old, and those with tetracycline allergy |
| STARI<br>*Borrelia lonestari* | *Amblyomma americanum* | • ECM in southern states. • Similar symptoms to Lyme disease, but less severe | | • Clinical<br>• PCR diagnosis reported once. | • Doxycycline<br>• Cefuroxime axetil<br>• Amoxicillin appears to not be effective as per one case report |
| Tick-borne Relapsing Fever<br>*Borrelia hermsii*<br>*Borrelia parkeri*<br>*Borrelia turicata* | *Ornithodoros* species | • Acute onset of a nonspecific febrile illness that recurs after defervescence. | Blood:<br>• Thrombocytopenia<br>• Coagulopathy<br>Urine:<br>• Hematuria, proteinuria | Direct visualization:<br>• Blood<br>• CSF<br>• Bone marrow<br>Immunofluorescence<br>PCR<br>Serology | • Tetracycline<br>• Ceftriaxone if neurological involvement<br>• Penicillin G or erythromycin for pregnant adults and children < 8 years of age |

cranial nerve, which can be bilateral), cerebellar ataxia, mononeuritis multiplex, and polyneuropathy (axonal sensorimotor neuropathy).[10] Optic nerve inflammation leading to blindness may occur in children,[7] and cases of pseudotumor cerebri as a presentation of Lyme disease have been reported in both children and adults.[11] A lumbar puncture in Lyme meningitis shows laboratory abnormalities similar to a viral infection.

*Early Cardiac Involvement.* Cardiac manifestations of Lyme disease occur weeks to months following the bite. There is a gender predilection for men (3:1 male to female ratio). Atrioventricular block is the most common conduction abnormality seen with Lyme carditis. It usually presents with a third-degree block, although second-degree and first-degree blocks (most common in children) occur. Escape rhythms, brief asystoles, and fluctuating bundle branch blocks portend a poorer prognosis. CHF, dilated cardiomyopathy, carditis, and non-sustained ventricular tachycardia are other cardiac manifestations of Lyme disease.[12]

*Late Disseminated.* Late Lyme disease occurs months to years following the initial infection. This clinical syndrome presents with arthritis, encephalopathy, and dermatologic changes. Arthritis presents with episodes of oligoarticular arthritis of large joints, most commonly affecting the knees. Patients present with an acutely inflamed joint, with aspiration showing elevated white blood cell counts ranging from 500-110,000 cells/mL with a PMN predominance, consistent with other inflammatory or infectious arthritides. Chronic central nervous system (CNS) findings of late Lyme disease include neuropsychiatric symptoms affecting mood, sleep, and memory. Encephalomyelitis, while rare, can lead to spastic quadraparesis or bowel/bladder dysfunction. Acrodermatitis chronica atrophicans is a dermatological complication of late Lyme disease that presents with insidious violaceous discolorations of the acral surfaces of arms or legs that causes sclerosis and atrophy over years. This is most often reported in women from Europe.[7]

**Diagnosis.** Lyme disease should be suspected in patients presenting with ECM or Lyme-associated symptoms such as unexplained heart block in patients who live in a location endemic to *I. scapularis.* A careful travel history or history of tick bites should be obtained in cases in which Lyme disease is suspected.

The presence of ECM in the setting of a consistent clinical history is the only manifestation of Lyme disease that is characteristic enough for it to be diagnosed without further laboratory testing. This must be differentiated from tick bite hypersensitivity reaction, which presents as an urticarial rash less than 5 cm at its greatest width that disappears over 1-2 days.

Serological testing, the diagnostic method of choice for Lyme disease, should be reserved for patients with a high clinical suspicion for Lyme disease, as they have a poor positive predictive value. The Centers for Disease Control and Prevention currently recommends a two-step approach to the diagnosis of Lyme disease.

Initial screening is performed with an ELISA, which is then confirmed with a Western blot. IgM antibodies are detectable in the first 1-2 weeks following exposure. Serological testing is highly insensitive in the first few week of infection, as antibodies may not have developed yet. In endemic areas, testing should be performed for coinfection with babesiosis and anaplasmosis.[13] CSF can be tested similarly if neurological involvement is suspected.[9] Other commercially available methods, including urine antigen testing, PCR, and immunofluorescent staining, are available, but their clinical usefulness has not been validated.[14]

**Treatment.** The recommended treatment regimen depends on the disease stage and patient characteristics. These recommendations are based on expert opinion.

*Early Localized or Disseminated Lyme Disease Without Neurological or Cardiac Involvement.* Oral doxycycline (100 mg BID), amoxicillin (500 mg TID), or cefuroxime axetil (500 mg BID) for 14 days are considered the first-line treatment choices. Doxycycline is often used in nonpregnant patients > 8 years of age, as it covers anaplasmosis and other rickettsial diseases that may co-infect or be confused with early manifestations of Lyme disease. Amoxicillin is recommended for pregnant patients or children younger than 8 years old. Cefuroxime can be used in penicillin-allergic patients.[15]

*Early Disseminated Disease: Neurologic Lyme Disease (Encephalitis, Meningitis, or Radiculopathy).* Intravenous ceftriaxone (2 g daily) for 14 days is recommended for adults with neurological Lyme disease. Cefotaxime or penicillin G are suitable alternatives. Oral doxycycline can be used (100-200 mg BID for 10-28 days) in patients who are intolerant of beta-lactams or those with isolated facial nerve palsy. This recommendation is similar for children.[15] These patients usually require admission to initiate intravenous antibiotics and to exclude other causes of meningitis.[13]

*Early Disseminated Disease: Lyme Carditis.* Patients who present with symptomatic cardiac disease (chest pain, dyspnea) or advanced heart block (first-degree with PR interval > 300 ms, second- or third-degree) should be admitted to the hospital and treated with intravenous antibiotics. The treatment regimen is similar to patients with early neurological Lyme disease (as above). Temporary pacemaker placement may be necessary, and consultation with a cardiologist should be pursued. Oral doxycycline is sufficient for minor cardiac involvement that is treated as an outpatient.[15]

*Late Disseminated Disease: Lyme Arthritis.* If there is no evidence of neuroborreliosis, oral doxycycline (100 mg BID) for 28 days is the recommended regimen for adults. Oral amoxicillin (first line in children younger than 8 years of age, and in pregnant women), and cefuroxime for 28 days may also be used.

If there is CNS involvement, patients of all ages should receive 2-4 weeks of intravenous ceftriaxone, cefuroxime, or penicillin G. Any patients who present with persistent joint swelling following therapy should be given another four-week course of oral antibiotics, or 2-4 weeks of intravenous ceftriaxone.[15]

*Late Disseminated Disease: Late Neurological Disease.* Treatment is similar to the treatment for early disseminated neurologic disease (see above). The recommended length of treatment is longer, at 2-4 weeks.[15]

*Prophylaxis.* Recent studies have demonstrated that a single prophylactic dose of doxycycline (200 mg PO) given within 72 hours of a known *I. scapularis* tick bite reduces the incidence of subsequent ECM, the only reliable clinical marker for Lyme disease (0.4% vs 3.2% for placebo).[17] As there are minimal adverse effects with this treatment, patients with known *I. scapularis* tick bite within the past 72 hours can be given a dose of this and provided close follow-up. If the tick bite is less than 36 hours old, no further prophylactic treatment is necessary following the removal of the tick. A vaccine was previously available, but this was discontinued in 2002 due to poor sales and questionable efficacy.[16]

*Chronic Lyme Disease.* Chronic Lyme disease is a syndrome in which persistent, nonspecific symptoms without medical explanation are attributed to this infection. Patients with a diagnosis of "chronic Lyme disease" may or may not have a history of a tick bite or acute Lyme disease. The current literature does not support the existence of a syndrome due to a persistent infection with *B. burgdorferi*. Nonetheless, many physicians and laypeople are convinced that it exists. It has led to patients being unnecessarily treated with long courses of intravenous antibiotics. Until there is further evidence to support its existence, chronic Lyme disease should not be an entity to work up or treat aggressively.[18]

***Summary of Lyme Disease***

- The most commonly reported vector-borne disease in the United States;
- Caused by the spirochete *B. burgdorferi*, transmitted by *I. scapularis*;
- Cutaneous, cardiac, musculoskeletal, and neurologic systems can be affected;
- Clinical diagnosis can only be made in the setting of ECM and appropriate history;
- In the absence of ECM, serology is often used to make the diagnosis;
- Treatment is with doxycycline in early disease for nonpregnant adults;
- Amoxicillin is used in pregnant women and children younger than 8 years of age;
- Intravenous ceftriaxone is generally used for disseminated disease;
- A single prophylactic dose of doxycycline 200 mg can be given to asymptomatic patients within 72 hours of *I. scapularis* bite.

## Anaplasmosis

*An 84-year-old woman from Long Island presents with worsening flu-like symptoms and confusion for the past 3 days. She developed fevers, myalgias, fatigue, nonproductive cough, and sore throat 3 days ago. This was initially thought to be due to a viral upper respiratory infection (URI), but the patient was brought in this morning when she was found lethargic and confused. On examination, the patient is febrile,*

*tachycardic, dehydrated, and ill-appearing. She has diffuse abdominal pain and meningismus.*

Anaplasmosis, also known as human granulocytic anaplasmosis (HGA), is caused by obligate intracellular, gram-negative coccobacilli called *Anaplasma phagocytophilum* that infects circulating leukocytes. It has previously been referred to as human granulocytic ehrlichiosis and human granulocytic anaplasmosis. The bacterium is related to the causative agent of human monocytic ehrlichiosis (HME). HGA and HME have similar clinical presentations. The characteristic finding of HGA is the presence of morulae within infected granulocytes.[19,20] This organism was first identified as the causative agent of HGA in 1994.[21]

**Epidemiology.** HGA is a zoonotic infection that is transmitted by *I. scapularis* and *I. pacificus*, the same vectors of Lyme disease and babesiosis. Its geographic distribution mimics that of Lyme disease. The number of reported cases of HGA has steadily increased since it became reportable. There were 348 reported cases in 2000 and 1761 in 2010. The case-fatality rate is about 1%. Its incidence is higher in older populations, and peaks in the mid-summer months.[22]

**Clinical Presentation.** Patients who are infected with *A. phagocytophilum* present 1-2 weeks following a tick bite with nonspecific systemic symptoms. These include fevers, headaches, myalgias, malaise, chills, gastrointestinal symptoms, and altered mental status.[23] These manifestations are usually mild to moderate in severity, and respond quickly to treatment. Spontaneous resolution is well documented. Diarrhea and rash are uncommon. Death usually occurs in immunocompromised or elderly individuals, often more than 10 days after onset of the disease. There have been reports of transmission via blood donors in China.[24] Fulminant infection with multiorgan system failure or meningoencephalitis leading to death is less frequent with HGA than it is with HME.

**Diagnosis.** The diagnosis of HGA is made based on clinical and laboratory findings. Basic laboratory tests are non-specific, and may show leukopenia, lymphopenia, thrombocytopenia, transaminitis, and elevated alkaline phosphatase. The quickest method of diagnosis is via direct examination of the blood smear, which will show the characteristic intracellular morulae. However, this test is often insensitive due to the scarcity of directly observable morulae. The most sensitive test is by performing an indirect immunofluorescence assay in the acute and convalescent phases of illness. Culture in malignant granulocytes (HL-60 line) and PCR are other diagnostic modalities.[15]

**Treatment.** Oral doxycycline 100 mg BID for 7-14 days is the standard treatment regimen for HGA. This is the recommended regimen in patients of all ages, as the benefit of treatment outweighs the risks in pregnant women and children. In addition, doxycycline covers other rickettsial infections (such as Rocky Mountain spotted fever, RMSF) that may present similarly to HGA.[23] Intravenous treatment is often indicated for hospitalized patients. There is limited evidence to suggest the use of rifampin to treat HGA in children and pregnant women; however, doxycycline is still the preferred antibiotic.[25] Levofloxacin has been shown to have activity against *A. phagocytophilum* in vitro, but there are no in vivo studies to suggest its use in infected patients.[15] There is usually prompt response to doxycycline. If a patient fails to improve, other diagnoses should be explored. Prophylactic treatment for HGA following a tick bite is not indicated, although it may be given to prevent Lyme disease.[23]

***Summary of Anaplasmosis:***

- Transmitted by the same vector as Lyme disease;
- *A. phagocytophilum* is an obligate intracellular organism that can be identified as intragranulocytic morulae on smear;
- Patients typically present with nonspecific symptoms
- Diagnosis is made with blood smear or serology;
- Treatment is with doxycycline for all patients;
- Rifampin, which does not cover other diseases caused by *I. scapularis*, can be considered in children and pregnant patients.

## Babesiosis

*The patient is a 32-year-old HIV-positive woman from Cape Cod who presents with jaundice for one day. She states that she has been having flu-like symptoms for the past 3 days. She noticed that her skin became yellow, she was very dizzy, and she felt progressively fatigued. She is febrile and hypotensive. On exam, she is has hepatosplenomegaly, jaundice, and diaphoresis.*

Babesiosis is a zoonotic infection caused by the intraerythrocytic protozoa of the genus *Babesia*. The first identified case of infection with *Babesia microti*, the primary organism that causes human babesiosis, in the United States occurred on Nantucket Island in 1969.[26]

**Epidemiology.** The epidemiologic data for babesiosis are limited, as national surveillance by the CDC did not begin until January 2011. Its primary vector is *I. scapularis*. Although initially called "Nantucket fever" due to the number of cases on the island, it is now known to occur throughout the distribution of the *Ixodes* tick. More than 100 species of *Babesia* are known to exist; however, only a few infect humans. *B. microti* causes the majority of babesiosis, mostly localized to the Northeast and Midwest. *Babesia ducani* and *Babesia divergens* have been identified as disease-causing agents on the West Coast and southern United States. There have been reported cases of transmission through blood transfusions.[26]

There were 1124 cases reported to the CDC in 2011. Ninety-seven percent of these cases were reported from Minnesota, Wisconsin, and five northeastern states. More than half of the cases were in individuals > 60 years of age, and the majority had symptoms starting in the mid-summer months. The male to female gender ratio was approximately 2:1. Ten cases were transfusion-related, and one reported case was thought to be congenitally acquired.[27]

**Clinical Presentation.** The clinical spectrum of babesiosis ranges from an asymptomatic, self-resolving infection to a fulminant, life-threatening disease. Symptoms develop after a 1-week to 1-month incubation period following a tick bite.[28] They occur as a result of hemolysis secondary to the reproduction of babesia within erythrocytes. Constitutional symptoms, including fever, fatigue, chills, and headache, are common. There may be concurrent photophobia, sore throat, and conjunctivitis. Abdominal symptoms, including pain, nausea, vomiting, and anorexia, are less frequent.[1] Similar to malaria, hemolysis occurs intermittently, corresponding to intermittent hemolytic anemia, sweats, myalgia, and headache.[20]

On exam, patients can have hepatosplenomegaly, joint swelling, jaundice, pallor, and dark urine. The acute illness lasts 1-2 weeks; patients may have fatigue that persists for months, and subclinical parasitemia can persist for months to years.[28] The acute illness can be complicated by multiorgan dysfunction. This includes DIC, liver failure, splenic rupture, ARDS necessitating intubation, renal failure requiring dialysis, congestive heart failure/myocardial infarction, and shock. Babesiosis appears to be most debilitating in the elderly, immunocompromised, and those who are functionally or anatomically asplenic. It is fatal in 5-9% of cases.[1,26,29]

**Diagnosis.** Babesiosis should be suspected in patients with a consistent clinical presentation and basic laboratory work consistent with hemolytic anemia (normocytic anemia with elevated reticulocyte count, elevated LDH, reduced serum haptoglobin), thrombocytopenia, and urinalysis with hemoglobinuria and proteinuria.[1,26] A definitive diagnosis can be established by observing the organisms on a Giemsa- or Wright-stained blood smear. The *B. microti* trophozoites are seen as pleomorphic intraerythrocytic rings that are indistinguishable from malaria trophozoites. The pathognomonic finding to clinch the diagnosis is the intraerythrocytic "Maltese cross," which is formed by tetrads of merozoites arranged in a cross-like pattern.[26]

The Maltese cross sign is rare, and may require multiple thick and thin blood smears to find. If the clinical suspicion remains high in the setting of multiple negative blood smears, detecting antibodies via indirect fluorescent antibody test can make the diagnosis. PCR of the patient's blood for *Babesia* species, and isolation of the organism by inoculating the patient's blood into hamsters or gerbils are other methods of diagnosis.[26,30]

**Treatment.** The treatment regimen of choice for mild to moderate babesiosis in immunocompetent patients is the combination of oral atovaquone (750 mg BID) and oral azithromycin (500-1000 mg on day one, then 250 mg daily) for a total course of 7-10 days. This regimen is the same for children, although it is dosed by weight. Immunocompromised patients may require a prolonged course of treatment lasting greater than 6 weeks. Intravenous clindamycin and oral quinine was previously the regimen of choice, but has been replaced due to significant side effects. This combination is reserved for severely ill patients.

Patients with moderate-to-severe babesiosis should be admitted to the hospital for monitoring and treatment. Those with high-grade parasitemia (> 10%), significant hemolysis, or renal/pulmonary compromise should undergo RBC exchange transfusions.[15,26] Treatment for coinfection with Lyme disease and anaplasmosis with doxycycline should be considered.

***Summary of Babesiosis:***

- Transmitted by the same vector as Lyme disease and anaplasmosis;
- *B. microti*, an intraerythrocytic parasite, is the main pathogen;
- Symptoms and laboratory findings are due to hemolysis and parasitemia (similar to malaria);
- Can lead to multi-organ failure and death, especially in the elderly and immunocompromised;
- Diagnosis is via blood smear showing "Maltese crosses" or via serology;
- Treatment is with oral atovaquone and oral azithromycin;
- Patients with severe illness require IV clindamycin and oral quinine.

## Tick-Borne Encephalitis

*A 19-year-old woman presents with a headache for 4 days associated with fever, nausea, vomiting, and worsening confusion. She is a student at West Point. She is febrile and hemodynamically stable. The exam reveals an ill-appearing woman with meningismus.*

There are multiple encephalitis-causing viruses in the genus *Flavivirus* transmitted by *Ixodes* and other ticks, which are collectively referred to as the tick-borne encephalitis (TBE) group. Other more well-known flavivirus species include the West Nile virus, yellow fever virus, and dengue fever virus. Tick-borne encephalitis is one of the most dangerous CNS infections in Europe and Asia. The aptly named tick-borne encephalitis virus is the culprit in at least 11,000 cases of TBE in Russia, and 3000 cases in the rest of Europe. Similar viruses spread *Ixodes* ticks are also known to cause fatal hemorrhagic fevers in Russia, India, and the Middle East.[31]

In the United States, the organisms responsible for all of the known cases of TBE are the Powassan virus (PV) and its close relative, the deer tick virus (DTV). DTV, which is serologically identical to but genetically different from PV, was isolated from the adult deer tick, *I. scapularis*, in 1997. PV has been found in other *Ixodes* species. These two viruses are highly similar in physical characteristics; however, they are often referred to as different entities in current literature.[32,33]

**Epidemiology.** Since its discovery in 1958, TBE (caused by DTV or PV) has occurred sporadically throughout the United States, Canada, and Russia. There have been approximately 70 reported cases of PV encephalitis and three reported cases of DTV encephalitis as of 2013. Most cases of PV encephalitis since 2010 were diagnosed in the states of Minnesota and Wisconsin. Two out of the three known cases of DTV encephalitis occurred in New York.

The general distribution of TBE appears to be in the northeastern/midwestern United States, corresponding to the distribution of *I. scapularis* and related species. Its incidence in the United States appears to be increasing, with 1.3 cases per year from 1999-2005, as opposed to 0.7 cases per year between 1958-1998. It is important to note that TBE reportedly due to PV may actually have been caused by DTV, as genetic sequencing was not employed to diagnose this condition in the past.[32,33]

**Clinical Presentation.** Infection by viruses of the tick-borne encephalitis group can present with a range from mild symptoms to meningoencephalitis leading to death. Following an incubation of 8-34 days, patients present with a prodrome of headache, lethargy, and confusion, leading to encephalopathy with various progressive neurological symptoms. Sudden onset of fever, nausea, and vomiting is characteristic. Overall, TBE is associated with 10% mortality and long-term neurological sequelae in half of survivors.[31,34]

In reported cases, CSF studies have shown findings consistent with aseptic meningitis. MRI has shown changes in the cerebellum, brain stem, and basal ganglia in patients with TBE. Biopsy (usually performed at autopsy) shows necrotizing meningoencephalitis with infiltrates of predominantly CD8+ cytotoxic T cells.[33,34]

**Diagnosis.** The diagnosis of TBE can be difficult, as it mimics the presentation of many viral, bacterial, or fungal meningitis/encephalitis. Testing for PV or DTV is not routinely indicated in patients presenting with encephalitis. However, several milliliters of CSF can be collected for further testing.[34] The diagnosis of TBE can be made with any of the following:[33]

- PV/DTV RNA presence in CSF;
- PV/DTV-specific IgM in CSF;
- Greater than fourfold increase in PV/DTV-specific neutralizing antibodies in serial serum assays;
- PV/DTV-specific IgM in serum *and* PV/DTV-specific neutralizing antibodies in the same or later serum specimen.

Although the definitive diagnosis cannot be made in the ED, some of these laboratory studies can be considered in the initial work-up of a patient presenting with meningitis or encephalitis.

**Treatment.** There is currently no standardized treatment regimen for TBE outside of supportive care. Pegylated interferon alpha and ribavirin have been administered with unclear results. Empiric treatment for patients presenting with TBE should be the same as for any patient presenting with meningitis or encephalitis, as TBE is relatively rare compared to other treatable causes of CNS infection. In current practice, this is with a combination of intravenous vancomycin, ceftriaxone, acyclovir, ampicillin, and dexamethasone, depending on the clinical context. Vaccines for TBE are available in Europe, but not in the United States.[34,35]

***Summary of Tick-borne Encephalitis:***

- Transmitted by the same vector as Lyme disease, anaplasmosis, and babesiosis;
- The known causative pathogens are closely related viruses in the genus *Flavivirus*;
- Rare, with about 70-80 total cases reported in the United States;
- Clinical/laboratory findings are similar to findings for other causes of viral meningoencephalitis;
- Diagnosis is via detection of viral genome or antibodies in the CSF;
- Treatment is supportive;
- Empiric treatment for other causes of meningitis should be implemented.

## *Dermacentor Variabilis*

*Dermacentor variabilis*, also known as the American dog tick, is the vector that is most commonly associated with the transmission of RMSF and tularemia. It is widely distributed on the West Coast, central-eastern United States, Mexico, and Canada.[36]

A related species, *D. andersoni*, known as the Rocky Mountain wood tick, is known to be the vector of the same diseases. It resides in the Pacific Northwest and northern Rocky Mountain states.

Only the adult form of the dog tick is thought to cause human disease. Adult ticks are most active in late spring through early fall, similar to other ticks. They occur primarily in the woods or areas with shrubs or long grass. Dog ticks are unable to establish an infestation within homes.[2,36]

Adult dog ticks are about one-quarter inch in length, reddish-brown in color, with a gray-silver colored marking on the dorsal surface (their "shield"). Male dog ticks have this marking diffusely on their dorsal surface, whereas the female dog tick's marking is localized to the cephalad one-third of its dorsal surface. This silver-gray dorsal scutum (which does not change while feeding) and the larger size of the dog tick help distinguish this tick from *I. scapularis*.[2,36]

## Rocky Mountain Spotted Fever

RMSF is now a member of a group of illnesses termed "spotted fever rickettsioses." They are a collection of diseases that are caused by the closely related *Rickettsia* species that are transmitted by various arthropod vectors. Other examples include typhus (in the United States and abroad) and rickettsialpox. *Rickettsia rickettsii* is an obligate, intracellular, gram-negative bacillus that infects endothelial cells within vasculature. Subsequent cytotoxicity causes its characteristic purpura.[1,28]

**Epidemiology.** *R. rickettsii* is transmitted by several species of ticks throughout the United States. RMSF cases have been reported in most of the contiguous United States. Although it is termed the "Rocky Mountain" spotted fever, its current incidence is highest in the south Atlantic states. The number of cases in the Rocky Mountain states dropped markedly in the 1940s for an unclear reason, and has remained so since. Its transmission can occur within 6-10 hours of tick attachment, and it may be transmitted by inhalation of contaminated aerosol in the laboratory setting.[37]

Until the early 2000s, there were roughly 600-1200 cases of RMSF

per year in the United States. This number has increased in the past decade, with 1791 cases reported to the CDC in 2009. The peak incidence is between April and October.[38] Outbreaks have been reported in areas where RMSF incidence is relatively rare, such as rural eastern Arizona, where the brown dog tick *Rhipicephalus sanguineus* is the implicated vector.[39] RMSF is considered the most fatal tick-borne infection. In the pre-antibiotic era, it was associated with a 65-80% case-mortality rate. It is associated with a 25% mortality if left untreated, but with antibiotics, the case-mortality rate is 0.5-3%.[1,38,40]

**Clinical Presentation.** Patients with RMSF present with symptoms about 2-14 days following the tick bite. The classic triad of fever, rash, and history of tick bite is only present in the minority of patients.[37] Initial symptoms of fever, headaches, and myalgias occur due to bacteremia. As the bacteria invade the vascular endothelium, necrotizing vasculitis ensues, with the appearance of the classic RMSF rash. This rash is described as discrete, blanching macules that appear 2-4 days following the onset of fever. It generally appears first on the wrists/ankles and quickly spreads to the soles/palms before migrating centrally onto the trunk. These macules slowly fade over 2-3 weeks. However, approximately 10% of patients with RMSF do not have a rash at any point in their disease course.[40]

The workup reveals lymphocytic pleocytosis in the CSF, anemia, thrombocytopenia, elevated liver tests, azotemia, and hyponatremia. Frank renal failure and CNS symptoms are markers of poor prognosis.[1,41] The clinical picture of RMSF may resemble meningococcemia, especially if patients present with meningismus. In these cases, the work-up and treatment should empirically cover both *R. rickettsii* and *Neisseria meningitidis.*

In some cases, the petechial lesions of RMSF form confluent ecchymotic areas of skin, often in the digits and genitalia. This may be complicated by necrosis with eventual gangrene.[40] Other complications include encephalitis, ARDS, cardiac arrhythmias, coagulopathy, and GI bleeding. Long-term issues are often due to CNS damage — neuropathy, cerebellar disorders, and neuropsychiatric symptoms. Without treatment (or delayed treatment), death can occur 1-2 weeks following the onset of fever. African-American men with G6PD deficiency have the most fulminant course.

**Diagnosis.** RMSF is largely a clinical diagnosis. Unfortunately, clinical findings in RMSF are largely nonspecific and are similar to the presentation of many tick-borne and non-tick-borne diseases.[41] Definitive diagnosis is made via serological tests or PCR, since *R. rickettsii* is notoriously difficult to culture. Antibodies cannot be detected for 7-14 days following the onset of illness. Currently, the gold standard test to diagnose RMSF is the indirect fluorescent antibody (IFA) test. Immunohistochemistry staining of skin biopsies can confirm the diagnosis. However, this is not widely available, and is more often used to confirm diagnoses at autopsy. PCR methods are available, but have poorer sensitivity than IFA.[1,41] It is currently recommended that empiric treatment be initiated if the clinical suspicion for RMSF is high, pending confirmatory test results at a future date.[42]

**Treatment.** There is a clear link between delay in treatment and mortality. This is evidenced by an increased mortality in those who present with a late-appearing rash, without a history of tick bite, or atypical symptoms of RMSF.[37] Beginning treatment more than 5 days following the onset of symptoms is associated with poorer outcome.[43]

The first-line treatment for RMSF is 7-14 days of doxycycline for both adults (100 mg BID) and children of all ages. Patients who are severely ill should be hospitalized and given intravenous doxycycline. An added benefit of doxycycline is that it covers other tick-borne organisms with clinical presentations that may be confused with RMSF.[1,42]

Chloramphenicol (50-75 mg/kg/day for 7 days) has anti-RMSF activity. However, its efficacy is inferior when compared to doxycycline, it has more side effects, and it has a more complex dosing schedule. It is recommended for pregnant patients and those with tetracycline allergies. However, doxycycline should be considered in pregnant patients with severe symptoms.[1,41] There is no evidence to support the use of post-exposure prophylaxis for RMSF.[42]

***Summary of Rocky Mountain Spotted Fever:***

- Most frequently occurs in the Atlantic states;
- It presents with a characteristic rash affecting the palms and soles that migrates proximally;
- Diagnosis and empiric treatment with doxycycline should begin based on clinical findings.

## Tularemia

Tularemia is an uncommon, potentially fatal zoonotic infection that is caused by a gram-negative coccobacillus *Francisella tularensis.*[44] It is considered a potential agent in biological weapons.[1]

**Epidemiology.** The primary tick vectors for tularemia in the United States include the dog tick, wood tick, and the lone star tick. However, it can be transmitted by other arthropods or via inhalation, laboratory exposure, ingestion of contaminated foods/water, or animal bites. More than 250 animal species are thought to be carriers of *F. tularenis.*[14]

Tularemia has been reported in every state in the United States except Hawaii. It is much more prevalent in south-central states; 56% of all cases in 2000 were reported from Arkansas, Missouri, South Dakota, and Oklahoma. Between 2003 and 2012, 95-166 cases per year have been reported in the United States. Like other tick-borne diseases, most cases were reported in the late spring to early autumn months. This disease is more prevalent in men and those with particular exposures (i.e., landscapers who cut up brush, mow lawns, etc.).[1,45,46]

**Clinical Presentation.** Tularemia presents with an abrupt onset of fever, anorexia, vomiting, chills, headache,

and myalgia following an incubation period of 1-21 days. One of the hallmarks of this disease is a high fever without a reflexive increase in pulse, a phenomenon known as pulse-temperature disparity. There are six syndromes that describe the different clinical manifestations of tularemia.[1,46]

• **Ulceroglandular (65-75% of all cases):** This form of tularemia occurs due to cutaneous exposure to *F. tularensis*, which can occur due to tick bites, direct exposure to animals while skinning/cleaning a carcass, or secondary to an animal bite. A pruritic/tender papule occurs at the site of injury, which progresses to an indurated, pustular, nonhealing ulcer with a punched-out appearance that later develops a necrotic base. Regional lymphadenitis occurs with the ulcer as the organisms migrate along the lymphatics. The lymph nodes may become fluctuant and drain suppurative fluid.[1,46]

• **Glandular (5-10% of all cases):** This form is similar to ulceroglandular tularemia, except lymphadenopathy occurs without the presence of the characteristic skin ulcer.[46,47]

• **Oculoglandular (approximately 1% of all cases):** This occurs when the portal of entry is the conjunctiva. Painful, purulent conjunctivitis ensues, with nodule formation and ulceration. Patients may present with only ocular symptoms before regional lymphadenopathy is present. Preauricular lymphadenopathy is unique to tularemia and helps distinguish it from other infectious diseases.[46]

• **Oropharyngeal (< 5% of all cases):** This syndrome occurs following ingestion of infected food or water. It presents as a febrile illness with exudative pharyngitis and oral ulcers. It can mimic URI.[1]

• **Typhoidal:** This syndrome is considered rare, but accounted for approximately 10% of all cases in one series.[47] This presents in older patients as a viral syndrome, which leads to sepsis, as it is the presentation of tularemic bacteremia. Blood culture growth, ulcers, and lymphadenopathy may be absent. Ultimately, this can lead to septic shock, and mortality is high without appropriate treatment.[46] Meningitis and pneumonia can complicate this syndrome.[48]

• **Pulmonary:** This syndrome occurs secondary to inhalation of infectious particles or via hematogenous spread to the lungs from cutaneous/lymphatic sources. It must be considered in the diagnosis in patients with an appropriate exposure history and atypical pneumonia unresponsive to conventional treatment. Patients present with dyspnea, hemoptysis, and/or chest pain. The chest X-ray is generally abnormal with infiltrates and/or pleural effusion.[46]

**Diagnosis.** Oropharyngeal swabs, sputum samples, or blood can be sent for culture. Cultures are often negative, and it may take up to 2 weeks to appear. In addition, laboratories must take special precautions to prevent personnel from being infected during the culture process.[48,49]

A presumptive diagnosis can be made with direct immunofluorescent antibody assay, latex/tube agglutination assay, or via a PCR. Immunohistochemistry of histological specimen can be used to directly visualize the bacterium.[1,49,50]

**Treatment.** Treatment recommendations for tularemia have been driven by cure/relapse rates seen in multiple case series and anecdotal data. Aminoglycosides, chloramphenicol, tetracyclines, and fluoroquinolones have been shown to be effective in tularemia. In general, streptomycin is the treatment of choice for severe tularemia that is not complicated by meningitis. Treatment is generally for 7-14 days. Gentamicin is a suitable alternative and is used preferentially over streptomycin.[49]

The FDA has approved tetracyclines as an alternative in patients with mild-to-moderate tularemia. The preferred regimen is doxycycline (100 mg BID) for at least 14 days. Although it is not FDA approved, oral ciprofloxacin has been shown to be effective in patients of all ages.[49,50] Chloramphenicol with streptomycin (or with gentamicin if streptomycin is not available) is used for tularemic meningitis. Chloramphenicol is generally not used as monotherapy for tularemia.[48]

The recommended post-exposure prophylaxis regimen for tularemia is oral doxycycline (100 mg BID) or ciprofloxacin (500 mg BID) for 14 days. This includes laboratory personnel, who may have direct exposure to the organism. Tularemia is not transmitted from person to person.[51]

**Implications for Public Health.** Tularemia caused major water-borne epidemics in Europe and Asia during the 20th century. The concern for the use of tularemia as a biological weapon surfaced following the events of 9/11. The Working Group on Civilian Biodefense recommended that in a mass-casualty situation, exposed patients should receive prophylactic doses of oral doxycycline or ciprofloxacin. Clothes and exposed skin should be washed with soap and water. Standard precautions should be employed in interacting with exposed patients.[51]

Although a biological attack with tularemia has not come to fruition, tularemia is a potential bioterrorism agent due to its extreme infectivity (inoculation of 10 organisms can cause disease), ease of dissemination, and capacity to cause extreme morbidity and mortality.

***Summary of Tularemia:***

• Widely prevalent — reported in almost all states, and epidemic throughout the world;

• Tularemia begins as a nonspecific illness, which progresses to one of six different syndromes;

• Most frequently, there is an ulcerative lesion with associated adenopathy;

• It is considered a potential biological weapon;

• Diagnosis is made by serology;

• Intravenous streptomycin is the treatment of choice.

## Colorado Tick Fever

Colorado tick fever is a viral illness caused by an RNA virus, Colorado tick fever virus (CTFV). The true reservoir for this virus is the wood tick, *Dermacentor andersoni*, and occurs in the western United States and southern Canada at an altitude of 4000-10,000 feet. Unlike Lyme disease or RMSF, a brief bite from a wood

tick is sufficient to transmit the virus. There are 200-400 cases of tick fever reported every year, most commonly in the summer months.[35,52]

**Clinical Presentation.** Following an incubation period of 3-5 days, CTFV causes a self-limited febrile illness including chills, headache, myalgia, and lethargy. Meningoencephalitis, hemorrhagic disease, pericarditis, myocarditis, orchitis, and pneumonia, although rare, have been reported. Rash is uncommon. Half of the patients will have symptoms that improve for 1-2 days followed by recurrence of fever ("saddleback fever"). The total duration of illness is usually 7-10 days. In Colorado, CTFV is much more common than RMSF.[52,53]

**Diagnosis and Treatment.** Laboratory testing shows leukopenia, thrombocytopenia, and the presence of atypical lymphocytes. Reverse transcriptase PCR can be used to detect the virus in the first week of symptoms, or serological tests can be performed (ELISA, fluorescent antibody tests) > 2 weeks after symptom onset. Viremia lasts approximately 4 weeks, which allows detection for a prolonged period of time. The infection is self-limited in humans. Treatment is supportive.[35,52,53]

***Summary of Colorado Tick Fever:***

- Causative pathogen is the Colorado tick fever virus;
- Presents as a self-limited febrile illness;
- Diagnosis is made by detecting viral genome in the patient serum or by serology;
- Treatment is supportive.

## Tick Paralysis

Tick paralysis, also referred to as tick toxicosis, causes ascending motor neuropathy with sensory sparing. The etiological agent is a toxin that is carried in the saliva of more than 40 species of hard-bodied ticks. In the United States, it is most commonly caused by *D. variabilis* and *D. andersoni*. Although it occurs throughout the United States, it is most prevalent in the Pacific Northwest, on the West Coast, and in the Southeast.[52,54]

Tick toxicosis is a rare condition. The true incidence is unknown since it is not a reportable disease. One series reported 33 cases over 60 years in Washington state. It preferentially affects young girls who are younger than 8 years old between the months of March and July. When found, ticks are often located on the scalp or along the hairline.[54]

**Clinical Presentation.** Five to seven days after tick attachment, tick paralysis presents with a prodrome of restlessness, irritability, lethargy, and weakness, followed by ataxia that progresses to symmetric, ascending flaccid paralysis. The disease course is acute, with progression to upper extremity, and respiratory weakness occurring over the course of 1-2 days. There is hypo/areflexia without any changes in mentation or sensory function. Ophthalmoplegia and bulbar dysfunction can occur. Without intervention, patients die of respiratory failure.

Patients are typically afebrile and have no CSF changes. Nerve conduction studies are consistent with demyelination and loss of motor axons.[52,54,55]

**Diagnosis and Treatment.** The identification and removal of the tick leads to rapid resolution of symptoms over 24-48 hours. This may require looking at the scalp using a fine-toothed comb and inspecting the axilla and perineum for the tick. The tick should be removed in the usual fashion. If necessary, supportive treatment with mechanical ventilation can be provided until the tick is found.[55]

***Summary of Tick Paralysis:***

- Caused by a toxin that is transmitted through the tick's saliva;
- Presents with a prodrome of ataxia, followed by ascending, flaccid paralysis;
- Diagnosis and treatment is by identifying and removing the tick.

## *Amblyomma Americanum*

*Amblyomma americanum*, the lone star tick, is primarily responsible for the transmission of human ehrlichiosis, also known as human monocytic ehrlichiosis (HME). In recent literature, it has been implicated in the Lyme disease-like illness known as southern tick-associated rash illness (STARI) and "meat allergy." It is primarily endemic to the southeastern to eastern parts of the United States.[3]

The lone star tick gets its name from the conspicuous spot on the dorsal surface of the female body. They feed on humans during all stages of life, allowing them to cause disease throughout the year. Unlike the bites of other disease-causing ticks, the bite of the lone star tick can cause significant irritation and pain.[2]

## Ehrlichiosis

Ehrlichiosis is a zoonotic disease that is clinically similar to anaplasmosis. It is caused by an obligate, intracellular, gram-negative organism. The lone star tick is the most common transmitter of *Ehrlichia chaffeensis*, although *D. variabilis* (the dog tick) has been implicated in areas where the lone star tick is not endemic. *Ehrlichia ewingii* is primarily transmitted by the lone star tick.[1,56,57]

The pathogenesis involves the infection and subsequent replication within human leukocytes by these organisms. *E. chaffeensis* primarily targets monocytes or macrophages (hence, HME), whereas *E. ewingii* targets granulocytes (similar to anaplasmosis). This is manifested by the presence of characteristic morulae within infected leukocytes.[56,57]

**Epidemiology.** HME caused by *E. chaffeensis* became a reportable disease to the CDC in 1999. Since then, its incidence has increased from 200 cases in 2000 to 740 cases in 2010. Its case-fatality rate has been between 1-4%. Most cases occur between April and September when the activity of the lone star tick is at its highest. It occurs more frequently in older men and in immunocompromised patients (especially HIV/AIDS, asplenic patients, and those on immunosuppressives).[1,58]

Ehrlichiosis caused by *E. ewingii* (also transmitted by the lone star tick) has only recently been reported in humans. The first cases were reported in four patients from Missouri in 1999. Three out of the four patients were on immunosuppressive therapy.[57] Four more cases were described

in patients from Tennessee and Oklahoma in 2001.[59] Since becoming a reportable disease in 2008, only nine cases of ehrlichiosis caused by *E. ewingii* have been reported to the CDC.[60]

**Clinical Presentation.** The clinical presentation of HME and *E. ewingii* ehrlichiosis is similar to HGA. Its onset begins 5-21 days following the tick bite as an undifferentiated febrile illness with abrupt fever, headaches, arthralgias, chills, and myalgias. Gastrointestinal symptoms such as nausea, vomiting, diarrhea, anorexia, and abdominal pain may also occur. Respiratory symptoms are less common. One-third of all patients ultimately develop a rash, usually 1 week into the illness. It is usually diffuse (sometimes affecting the palms and soles) and petechial, maculopapular, or erythematous.[1,60]

Laboratory studies consistent with ehrlichiosis include pancytopenia and elevated liver transaminases. Thrombocytopenia is the most common finding. The leukopenia is characterized by early lymphopenia, followed by lymphocytosis. Anemia occurs 2 weeks after onset. Other laboratory findings include azotemia, electrolyte abnormalities, elevation in LDH, and elevated amylase. Approximately 60-70% of patients require hospitalization. Severe complications include ARDS, renal failure, aseptic meningoencephalitis, myocarditis, GI bleed, and DIC. A toxic shock-like syndrome may occur in HIV-infected patients. In general, complications are more frequent in the immunocompromised.[1,59]

**Diagnosis.** The diagnosis of ehrlichiosis in the acute setting is made clinically. Patients often don't remember a tick bite. Empiric treatment should be started prior to confirmatory testing.

The quickest way of diagnosing ehrlichiosis is via thick and thin peripheral blood smears on a Wright or Giemsa stain. The presence of intracellular morulae confirms the diagnosis. The sensitivity is rather low at 2-38%. The most sensitive test in the acute phase of the illness is the PCR assay. In the following weeks, the PCR assay declines in sensitivity, and indirect immunofluorescence assay (IFA) becomes the preferred diagnostic technique. PCR and IFA are usually used in conjunction to diagnose ehrlichiosis. Lastly, culture can be used in diagnosis. *E. chaffeensis* can be visible in leukemic cells (HL-60 line, similar to culture for anaplasmosis) in 2-36 following inoculation. *E. ewingii* has not been grown in laboratory as of 2010.[1,60,61]

**Treatment.** The first-line treatment for ehrlichiosis is doxycycline for 7-14 days in both adults (100 mg BID) and children. Treatment should begin as soon as the diagnosis is clinically suspected. If symptoms do not improve in the first few days, an alternative diagnosis should be pursued. Rifampin has been shown to be effective in some patients, although the data are less robust compared to doxycycline. It may be considered in pregnant patients, children younger than the age of 8 years, and those with a tetracycline allergy. Prophylactic therapy for asymptomatic patients with a history of tick bite is not recommended.[60,61]

***Summary of Ehrlichiosis:***

- *E. chaffeensis* is an obligate intracellular organism that can be identified as intramonocytic morula on smear;
- Patients typically present with nonspecific symptoms, similar to anaplasmosis;
- Diagnosis is made with blood smear, PCR, or via serology;
- Treatment is with doxycycline for all patients.

## Southern Tick-Associated Rash Illness

Since the mid-1980s, multiple patients in the south-central and southeastern United States have presented with ECM and flu-like symptoms without evidence of *B. burgdorferi* infection. This Lyme disease-like disease was later associated with the bite from the lone star tick. *Borrelia lonestari*, a spirochete that is molecularly distinct from *B. burgdorferi*, is now thought to be the causative agent of a disease entity known as STARI. This is also known as Master Disease and Southern Lyme disease.[1,62]

**Epidemiology.** Cases of STARI have been reported in Alabama, Missouri, Georgia, South Carolina, North Carolina, and possibly Maryland. The exact number of cases is unknown, as the disease is not reportable. It is much more prevalent in the Southeast than Lyme disease. What is known is that approximately 1-3% of lone star ticks are infected with a spirochete, and that *B. lonestari* has been detected in lone star ticks in Southeastern and Mid-Atlantic states.[1,62,63]

**Clinical Presentation.** The presence of an ECM-like rash is characteristic of STARI. In comparison to Lyme disease, the rash of STARI tends to be smaller, with fewer lesions, and is more likely to have central clearing. However, at initial presentation, the rash may be indistinguishable from that of Lyme disease. STARI may present as a nonspecific febrile illness with headache, fever, myalgia, and arthralgia.[63] It is less likely than Lyme disease to present with systemic findings such as meningeal signs, neuropsychiatric symptoms, or regional lymphadenopathy. There are no known late complications of STARI.[62]

**Diagnosis.** The presence of an ECM-like rash and history of exposure to a tick in the Southeastern parts of the United States is sufficient to make a diagnosis. However, Lyme disease should be considered first if the patient has been in an endemic area. There is no serological test to diagnose STARI. There is only one case report describing the detection of *B. lonestari* via PCR in a skin biopsy of an ECM-like skin lesion in a patient bitten by the lone star tick. The spirochete has been cultured from the lone star tick, but has never been cultured from a human.[62,63]

**Treatment.** As there is no way to clinically distinguish the rash of STARI from Lyme disease, empiric treatment with doxycycline, amoxicillin, or cefuroxime as indicated for Lyme disease should be initiated in patients at initial presentation.[62] A case report demonstrated that STARI

completely resolved in an adult man following a course of doxycycline 100 mg BID for 14 days.[64]

***Summary of Southern Tick-associated Rash Illness:***

- Thought to be caused by *B. lonestari*, a bacterium similar to the causative agent of Lyme disease;
- Presents similar to Lyme disease with ECM, but has less severe symptoms;
- It is more prevalent than Lyme disease in the southeastern states;
- Diagnosis is made clinically;
- Empirically treat as if it were Lyme disease with doxycycline, amoxicillin, or cefuroxime.

## The Lone Star Tick and Allergies to Meat

Allergy to red meat is a relatively uncommon food allergy. It is unique in that symptoms may arise hours following the ingestion of the allergen.[65] IgE to galactose-alpha-1,3-galactose (alpha gal), a disaccharide found in the cells of nonprimate mammals, has been found in individuals with meat allergies.[66]

It has recently been hypothesized that exposure to tick salivary proteins can cause a cross sensitization to alpha gal. In the Southeastern United States, the bite from a lone star tick appears to precede the development of an allergy to red meat. A similar correlation between tick bites and red meat allergies have been demonstrated in other areas around the world, including Europe and Australia.[65,66]

## Ornithodoros Species: Soft-bodied Ticks

"Soft-bodied" ticks belong to the genus *Ornithodoros.* They are different from the hard-bodied ticks described in previous sections in that their bites are usually brief (< 30 minutes). They live within rodents' dwellings, and humans come into contact with them when they sleep in rodent-infested buildings. Because these ticks have life spans in the range of 10-20 years, a home can remain permanently infested unless steps are taken to eradicate the rodent burrow.[67] In the United States, ticks from this genus are the vectors that transmit tick-borne relapsing fever (TBRF).

There are three species of *Ornithodoros* in the United States that are responsible for the cases of TBRF. *Ornithodoros hermsii* and *Ornithodoros turicata* cause the most cases. *Ornithodoros parkeri* is a less common transmitter of TBRF. *O. hermsii* and *O. parkeri* are typically found in the coniferous forests of mountainous regions in the western United States at elevations of 1500-8000 feet. *O. hermsii*, the most common vector, preferentially feed on humans that come into close contact with their natural hosts, small rodents, near freshwater lakes. *O. turicata* is found in the drier regions in south-central United States, often in caves.[1,68]

## Tick-borne Relapsing Fever

In the United States, the three *Borrelia* species that cause TBRF are named after the tick that carries it: *Borrelia hermsii*, *Borrelia parkeri*, and *Borrelia turicata*. Relapsing fever in other parts of the world is transmitted by ticks or by the human body louse (louse-borne relapsing fever, LBRF). LBRF is an important cause of morbidity and mortality in crowded areas of the world with poor hygiene and nutrition.[68] LBRF is caused by another *Borrelia* species, *Borrelia recurrentis.*[69]

Relapsing fever is an aptly named disease; it is characterized by recurring episodes of a nonspecific febrile illness. This occurs because the *Borrelia* organisms repeatedly change their surface antigen in response to selection pressure within the host. This leads to repeated episodes of spirochetemia, which repeatedly stimulate the host immune system into producing recurrent episodes of a febrile illness.[69]

**Epidemiology.** TBRF is found throughout the Americas, Europe, Asia, and Africa. In the United States, it is endemic to the Western states and the southcentral regions. The most common exposure sites are limestone caves of Texas and the forests of the major mountain ranges in the West, including the Cascades, Rockies, and Sierra Nevada ranges. It is typically not reported east of Texas, and only one case in Wyoming.[69]

A total of 450 cases of TBRF were reported between 1977 and 2000. This is likely an underestimation of its true incidence. Its peak incidence occurs between November and January in Texas, and between June and September in the rest of the Western United States.[1,68] Isolated cases of transmission through blood transfusions, IV drug use, and laboratory work have been reported.[69]

**Clinical Presentation.** Relapsing fever presents as an acute-onset febrile episode associated with nonspecific symptoms, including chills, headache, myalgia, arthralgia, nausea, vomiting, and abdominal pain. This follows an incubation period lasting an average of seven days. Patients are rarely aware of the tick bite. The febrile episode ends with "crisis" consisting of two phases. During the "chill phase," patients experience a fever that may be as high as 41.5° C associated with an altered mental status, tachypnea, and tachycardia, which lasts 10-30 minutes. This is followed by a "flush phase," with diaphoresis, normalization of body temperature, and transient hypotension. The entire febrile episode lasts 3 days on average. An afebrile period of approximately 7 days associated with fatigue occurs before another febrile episode occurs. Subsequent episodes tend to be less severe. Without treatment, three to five febrile episodes occur before the disease resolves. Some patients may present with a petechial or maculopapular rash, meningeal signs, and hepatosplenomegaly. Neurological complications (meningismus, cranial nerve palsies) are more frequent with *B. turicata* infections than with other causes of TBRF. Laboratory work-up tends to be nonspecific, and thrombocytopenia, hematuria, proteinuria, hyperbilirubinemia, and mild coagulopathy are the most common findings.[1,70]

Severe complications related to TBRF include ARDS, renal failure, myocarditis, anterior uveitis, and meningitis. There is no association between hemorrhage and the

thrombocytopenia seen in TBRF. Death due to TBRF in the United States is rare, and it typically affects newborns of mothers affected with relapsing fever.[69]

**Diagnosis.** Visualizing the *Borrelia spirochetes* on a smear of the peripheral blood, bone marrow, or CSF of an infected patient confirms the diagnosis of TBRF. The appearance of the spirochetes on Wright/Giemsa stain or dark field microscopy is morphologically similar to the *B. spirochetes* seen in Lyme disease. The sensitivity of this test is highest during the first febrile episode.[70] Other methods include direct/indirect immunofluorescence staining of the *Borrelia*, or by inoculating patients' blood into mice to amplify the number of spirochetes. There are only a few laboratories capable of performing serological tests to confirm the diagnosis, and this test is marred by poor specificity.[69]

**Treatment.** Tetracycline 500 QID for 10 days (IV if PO is not tolerated) is the recommended treatment regimen for adults. Erythromycin can be used if tetracyclines are contraindicated. Intravenous ceftriaxone (2 grams per day for 10-14 days) is recommended for patients with CNS involvement. Children younger than 8 years old and pregnant patients should be treated with IV penicillin G (600,000 IU daily) or erythromycin (500 mg QID).[69,70]

Patients should be monitored for the first 2-4 hours of treatment for Jarisch-Herxheimer reaction (JHR), reported to occur in 54% of patients who were treated for TBRF.[71] This presents with elevation of body temperature, hypotension, chills, and rigors. JHR occurs due to a massive cytokine release that occurs as the spirochetes clear from the circulation. Although no deaths due to JHR in patients with TBRF have been reported, patients with this reaction should be monitored closely.[69] Post-exposure prophylaxis with a 5-day course of doxycycline (200 mg first day, 100 mg for the following 4 days) is efficacious in preventing TBRF in patients with a presumed exposure.[72]

***Summary of Tick-borne Relapsing Fever:***

- Most prevalent on the West Coast and south-central United States;
- Presents with multiple episodes of nonspecific febrile illness. This may be complicated by multi-organ dysfunction;
- Diagnosis is via direct visualization of *B. spirochetes* on body fluid smear or via serology;
- Tetracycline is the recommended treatment for nonpregnant adults;
- Penicillin G is recommended for children younger than 8 years old and pregnant women.

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## CME Questions

1. Which of the following is true regarding Lyme disease?
   a. The absence of a tick bite on history excludes Lyme disease.
   b. Lyme disease can be present without the characteristic rash on history or exam.
   c. Laboratory confirmation is necessary before treating patients dwelling in an endemic area presenting with erythema chronicum migrans (ECM) and a clinical history consistent with Lyme disease.
   d. Chronic Lyme disease is an established entity that should be aggressively pursued and treated in the ED.
   e. Fatigue and lethargy are rarely reported in patients with early disseminated disease.
2. A patient presents two days after hiking in Long Island. He has a tick attached to his lower leg. Which of the following is the correct treatment?
   a. Remove the tick by twisting off counter-clockwise.
   b. Remove the tick by twisting off clockwise.
   c. Remove the tick by pulling it straight out.
   d. Burn the tick off using a match.
3. Patients who present with a tick bite within 72 hours should be treated with which of the following?
   a. Amoxicillin for 5 days
   b. Doxycycline single dose
   c. Doxycycline for 10 days
   d. Rifampin for 20 days
4. An otherwise healthy male presents after a routine ECG showed third-degree heart block. Which of the following is most likely the cause?
   a. Lyme disease
   b. Anaplasmosis
   c. Babesiosis
   d. Tick-borne encephalitis
5. Where is Rocky Mountain spotted fever most common?
   a. Colorado
   b. Rocky Mountains
   c. Southeastern United States
   d. Long Island
6. Which of the following is true regarding Rocky Mountain spotted fever?
   a. The dog tick is the only established vector.
   b. Clinical suspicion should always be confirmed with laboratory tests prior to treatment.
   c. There is a clear link between delay in treatment and mortality.
   d. The triad of fevers, rash, and history of tick bite is present in the majority of patients.
7. Infection with which of these ticks is associated with the development of allergy to red meat?
   a. Dog tick
   b. Wood tick
   c. Lone star tick
   d. Tick

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**GST Registration No.:** R128870672

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