



Tick trouble: Overview of tick-borne diseases

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■ ABSTRACT

Tick-borne diseases can be severe or even fatal, but when identified early, most can be easily treated. Tick-borne diseases often present with nonspecific symptoms. Therefore it is important for the primary care physician to be familiar with the epidemiology of these diseases and their presentations. Although Lyme disease is the most common and well-known of the many tick-borne diseases, Rocky Mountain spotted fever, ehrlichiosis, and babesiosis are also threats throughout the United States.

AS SUBURBS EXPAND and deer populations continue to increase, more Americans are coming into contact with rural problems such as tick-borne disease. Caused by microorganisms endemic among white-tailed deer, white-footed mice, or other mammals, these diseases may be transmitted to humans through the bite of several species of ticks.

Identifying tick-borne diseases is difficult for three reasons. First, tick-borne diseases often present with nonspecific symptoms that can be confused with a wide variety of unrelated illnesses. Second, many patients never know that they have been bitten. Even though ticks may remain attached for hours or days, they are tiny, their bites are painless, and they seek out hidden locations such as the axilla and the groin. Third, although serologic tests are available, they generally do not become

positive until several weeks after the patient has been infected; therefore, these tests must be used for confirmation, not screening.

It is important for physicians to learn about the varying clinical characteristics and the epidemiology of these diseases. In this article, I will first call attention to three of the less familiar tick-borne diseases: Rocky Mountain spotted fever, ehrlichiosis, and babesiosis. I will conclude with an update on the most common of the tick-borne diseases, Lyme borreliosis.

■ ROCKY MOUNTAIN SPOTTED FEVER

An acute febrile illness, Rocky Mountain spotted fever is caused by *Rickettsia rickettsii*, a gram-negative intracellular bacillus transmitted by tick bites. The disease is misnamed: not all patients develop rash, and fewer than 2% of cases occur in Rocky Mountain states.

Symptoms and course. The onset of symptoms begins 4 to 14 days after exposure (mean, 7 days). Almost all patients have fever. Headache, rash, or myalgia is experienced by 80% or more of patients. Between one third and two thirds of patients experience abdominal pain, nausea, or vomiting. However, the classic triad of fever, headache, and rash is experienced by only about half of patients. The characteristic rash, which is not pruritic or painful, develops as macular lesions 3 to 5 days after the onset of the illness, progressing to maculopapules and petechiae. Starting on the wrists and ankles, it spreads to the palms and soles and then to the trunk. Between 9% and 16% of patients never experience a rash.

In severe cases, patients may enter delirium, shock, and renal failure. Mortality is about 5%, being highest in older patients,

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men, blacks, and those who do not receive prompt treatment.

Epidemiology and demographics. Rocky Mountain spotted fever has been reported in 48 states of the United States, Mexico, and Central and South America. About half of the 600 American cases every year occur in North Carolina, South Carolina, Tennessee, or Oklahoma. Although cases may occur at any time of year, about 90% of them occur between April and September during peak tick season. The age distribution of patients is bimodal, with most cases occurring among children age 5 to 9 years or among adults older than 60. The disease is somewhat more common among men than women (1.7 to 1) and in whites than in blacks. Only about two thirds of patients recall the tick bite.

Differential diagnoses include measles, meningococemia, influenza, enterovirus, leptospirosis, mononucleosis, viral hepatitis, typhoid fever, or idiopathic or thrombotic thrombocytopenia purpura. Rocky Mountain spotted fever may also resemble another tick-borne disease, ehrlichiosis.

Diagnosis should be made on the basis of clinical symptoms and a careful patient history searching for any recent tick bites or outdoor activity. Serologic tests can identify antibodies to the rickettsial organism, but only after 7 to 10 days of infection; therefore, these tests are best used for confirmation after treatment has already begun.

Laboratory tests are not particularly helpful. Although most patients become mildly anemic, and some may have some thrombocytopenia, hyponatremia, or elevated liver enzymes, these changes are not frequent enough or severe enough to be diagnostic. An elevation in white blood cell counts at the beginning of the disease resolves quickly.

Treatment. Doxycycline is the preferred treatment. It is also effective against ehrlichiosis, with which Rocky Mountain spotted fever may be confused. Tetracycline may also be used. Chloramphenicol is recommended for children and pregnant women.

■ EHRLICHIOSIS

Ehrlichiosis is an acute, febrile, multisystem disease with nonspecific symptoms that make

it difficult to diagnose.

The Ehrlichia organisms, members of the Rickettsiaceae family, are gram-negative, intracellular pleomorphic bacilli. The disease has two forms: *human monocytic ehrlichiosis*, found in the southeastern states, and *human granulocytic ehrlichiosis*, found in the Northeast, Midwest, and the West. The diseases, although clinically indistinguishable, are caused by different organisms and carried by different species of ticks, with white-tailed deer and white-footed mice as reservoirs.

Symptoms and course. More than 60% of those infected may be asymptomatic. Symptoms, when they do develop, begin 7 to 14 days after exposure. Virtually all symptomatic patients have fever, and up to 85% have headache. Myalgia, malaise, and nausea are common. One third of patients with human monocytic ehrlichiosis and 2% to 11% of those with human granulocytic ehrlichiosis have a truncal rash, most commonly maculopapular, distinguishing it from Rocky Mountain spotted fever. The rash rarely affects the hands and feet. In fatal cases, an association has been noted with opportunistic infections, leading to the possible conclusion that ehrlichiosis may cause some degree of immunosuppression.

Severe disease may be characterized by seizures, coma, and renal, respiratory, and cardiac failure, with mortality between 2% and 10%.

Characteristic laboratory findings are the combination of leukopenia, low platelet counts, and elevated hepatic enzymes. About half of patients become anemic. Blood samples from some patients will also have leukocytes with characteristic black spots called morulae, intracellular cytoplasmic vacuoles occupied by Ehrlichia organisms.

Epidemiology and demographics. Like other tick-borne diseases, ehrlichiosis can occur at any time of year but is most common between April and September. It is more common in men than women and is most frequent between the ages of 43 and 60. About two thirds of patients recall being bitten by a tick. The tick must be attached for 24 to 48 hours to transmit the disease; therefore, daily tick checks can be an effective means of prevention.

Serology is used to confirm, not diagnose, tick-borne disease

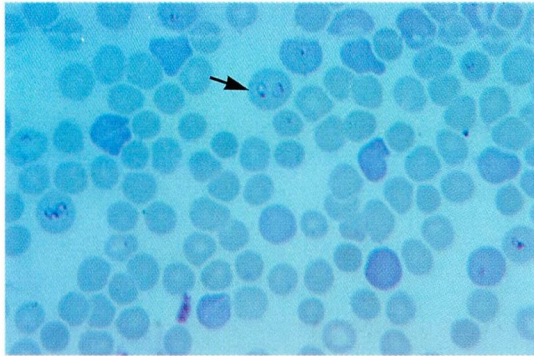


FIGURE 1. Blood smear from a patient with babesiosis. Note the infected red blood cells bearing the characteristic ring forms of *Babesia microti* (arrow).



FIGURE 2. Erythema migrans, the characteristic lesion that develops soon after being bitten by a tick infected with *Borrelia burgdorferi*, the causative agent of Lyme disease.

The Lyme disease vaccine is not approved for children

Differential diagnosis. This disease may resemble Rocky Mountain spotted fever, thrombotic thrombocytopenia purpura, hematologic malignancy, hepatitis A, pneumonia, or viral diseases such as mononucleosis.

Diagnosis. Clinical findings, including leukopenia and thrombocytopenia, with a patient history of tick bite or possible tick exposure, are important. Morulae are characteristic but do not occur in many patients and are difficult to recognize by the unsuspecting microscopist. Serologic testing can detect antibodies to human monocytic ehrlichiosis after 2 to 3 weeks of infection.

Treatment. Doxycycline is the treatment of choice, but chloramphenicol and rifampin are also effective.

■ BABESIOSIS

A zoonotic infection caused by an intraerythrocytic protozoan, babesiosis is suspected to have affected humans and cattle since Biblical times. In North America, the disease is transmitted by several species of ticks, and the reservoirs are again white-footed mice and white-tailed deer.

Symptoms and course. The incubation period ranges from 1 to 6 weeks. About 90% of patients experience fever with drenching sweat. Nausea, headache, and myalgia are also common, and some patients also experience arthralgia. Mortality is about 5%.

Epidemiology and demographics. The lack of national reporting requirements makes it difficult to determine the exact

range of the disease, but it appears to be most common in the Northeast, upper Midwest, and West, with concentrations on Shelter, Block, and Fire Islands in New York State. Peak incidence occurs in June and July, but the disease may occur from May to September. The seroprevalence of babesiosis in endemic areas is 9% to 21%, indicating that many exposed to the disease are asymptomatic. It is more common among men than women, and most common among those between ages 40 and 50. Fewer than 10% of patients recall a tick bite.

Differential diagnosis. The severe fever of babesiosis once led it to be called North American malaria, but true malaria is characterized by periodic fevers. Other differential diagnoses are drug reactions, sickle cell crisis, thrombotic thrombocytopenia purpura, *Escherichia coli* O157:H7 infection, mononucleosis, brown recluse spider bite, and mycoplasma or viral infections.

Diagnosis. A careful history focusing on possible exposure to ticks is important. A blood smear may show parasitemia, with the organisms forming characteristic ring forms and x-shaped “Maltese crosses” within erythrocytes (FIGURE 1). Serology generally shows antibodies only after 7 to 10 days of infection. Patients typically exhibit hemolytic anemia and elevated liver enzymes. A few patients have thrombocytopenia or leukopenia.

Treatment. Clindamycin, quinine, atovaquone, and azithromycin are all effective therapies.



■ LYME DISEASE

Although Lyme disease may have occurred in the 19th century, it was named in the 1970s after an outbreak in Old Lyme, CT. This multisystem inflammatory disease is the most frequent vector-borne disease in the United States. In 1998, 16,000 cases were identified.

The disease is caused by *Borrelia burgdorferi*, a slow-growing motile, flagellated spirochete that is endemic among many white-tailed deer and white-footed mouse populations. It can be transmitted to humans through the bite of an infected tick from the *Ixodes* genus.

Symptoms and course. Lyme disease is not transmitted unless the infected tick has remained attached for 36 hours or longer. The disease goes through three stages if untreated. In stage 1 disease, most patients develop erythema migrans, the characteristic round or oval expanding lesion around the tick bite which sometimes clears in the middle to form a bull's-eye (FIGURE 2). The lesion, which is not usually pruritic or painful, spontaneously resolves in 1 to 4 weeks without treatment. During this stage, many patients experience flulike symptoms: fatigue, headache, fever, and muscle aches are all common. Adenopathy is found in 23% to 40%. The onset of stage 1 symptoms occurs after an incubation period of 4 to 30 days.

Stage 2 Lyme disease, which develops in untreated patients after 1 to 4 months, may include symptoms that may be neurologic (Bell palsy), cutaneous (secondary erythema migrans), rheumatic (intermittent, asymmetric joint stiffness, swelling, and pain), or cardiac (atrioventricular block, myopericarditis). Patients often experience headache, musculoskeletal pain, and fatigue.

Untreated or inadequately treated Lyme disease may then enter stage 3. Patients may develop intermittent attacks of chronic inflammatory arthritis, often in the large joints. Encephalopathy or encephalomyelitis may also occur. Chronic neurological involvement may develop months to years after infection. Despite the vast array of manifestations, Lyme disease is rarely a fatal disease.

Patients showing signs of the later stages of disease may not have experienced any of

the earlier stages. It is of interest to note that European forms of borrelial infection show somewhat different patterns of signs and symptoms, with cutaneous and cardiac symptoms being more frequent.

Epidemiology and demographics. Lyme disease has been reported in 48 states, but 90% of cases occur in New England, the upper Midwest, and northwestern California. Lyme disease is most common from May to November. The age distribution is bimodal, with peaks between 5 and 9 years and then 30 to 59 years of age. It is more common in men than women.

Differential diagnosis. The list of differential diagnoses is vast and may include spider bite, urticaria, reactive arthritis, scleroderma, multiple sclerosis, chronic fatigue syndrome, fibromyalgia, and other disorders.

Diagnosis. Again, a history of a tick bite in an endemic area should prompt consideration of tick-borne disease. The erythema migrans lesion is characteristic. Serologic testing should begin with ELISA, followed by a Western blot for confirmation. Unfortunately, false-positive tests are common, and patients who have already begun treatment may display false negatives. *Borrelia* can be cultured from erythema migrans biopsies, but requires a special bacteriological medium. Newer polymerase chain reaction (PCR) tests are not reliable or standardized at this time.

Treatment. Prophylactic antibiotic treatment after tick bites is not recommended. Early-stage Lyme disease can be treated with oral antibiotics, but disease that is permitted to progress may require more intensive therapy including intravenous antibiotics. Doxycycline, amoxicillin, cefuroxime, ceftriaxone, and penicillin are all effective therapeutic options.

Vaccine. A vaccine against Lyme disease, LYMERix (SmithKline Beecham Pharmaceuticals), was approved in 1998 for individuals between 15 and 70 years of age. (A second vaccine, ImuLyme, from Pasteur Merieux Connaught, has not yet been approved.) LYMERix uses a unique mechanism of action: antibodies produced in response to the vaccine are transmitted to the tick from the human host during its blood meal. Once ingested, the antibodies kill the *Borrelia*

Prophylactic antibiotics are not recommended after a tick bite



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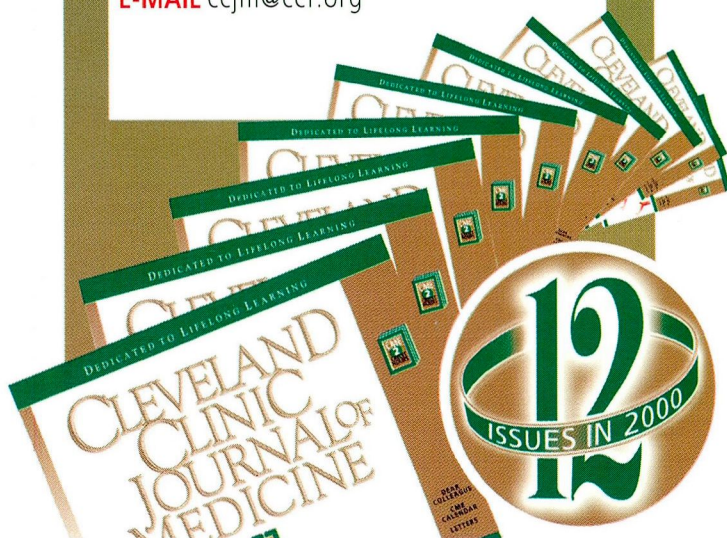
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organism in the tick's gut. Three doses over a 1-year period are required for 80% efficacy. Many questions remain about this vaccine, including its duration of effectiveness and whether it is safe in children, who represent one of the largest populations of Lyme disease patients. The vaccine has not been tested in pregnant women.

A careful risk assessment is necessary before recommending the vaccine. Those at high risk of tick bites are people who hike, camp, hunt, or work (for example, as park rangers or foresters) in wooded or overgrown areas known to be infested with ticks, particularly in spring and summer. The vaccine should not be used as an excuse to reduce personal protective measures against tick bites (see "Avoiding Tick Bites," page 249). It has been proposed that the vaccine might stimulate autoimmune reactions in some people with treatment-resistant Lyme arthritis; therefore, at this point, it is not indicated for these patients.

FURTHER READING

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CME ANSWERS



Answers to the CREDIT TEST on page 303 of this issue

- 1 B 2 A 3 E 4 A 5 B 6 D 7 E 8 C 9 D 10 E
 11 B 12 A