


# When to Suspect and How to Monitor Babesiosis

ELEFThERIOS MYLONAKIS, M.D., Massachusetts General Hospital, Boston, Massachusetts

In the past decade, cases of babesiosis in humans have been reported with increasing frequency, especially in the northeastern United States. *Babesia microti* (in the United States) and bovine strains (in Europe) cause most infections in humans. Most cases are tick-borne, although cases of transfusion-associated and transplacental/perinatal transmission have also been reported. Factors associated with more severe disease include advanced age, previous splenectomy and immunodeficient states. Symptoms include high fever, chills, diaphoresis, weakness, anorexia and headache. Later in the course of the illness, the patient may develop jaundice. Congestive heart failure, renal failure and acute respiratory distress syndrome are the most common complications. Therapy using the combination of quinine sulfate and clindamycin was the most commonly used treatment; however, atovaquone suspension plus azithromycin was recently reported an equally effective and less toxic therapy. Exchange transfusion, together with antibabesial chemotherapy, may be necessary in critically ill patients. (Am Fam Physician 2001;63:1969-74,1976.)

 A patient information handout on babesiosis, written by the author of this article, is provided on page 1976.

**B**abesiosis is a worldwide tick-borne hemolytic disease that is caused by intraerythrocytic protozoan parasites of the genus *Babesia*. The book of Exodus refers to a plague of “murrain” (hemoglobinuria) among cattle and other domestic animals. Possibly, this biblical reference was the first historical mention of babesial infection.<sup>1-3</sup> Intraerythrocytic piroplasms consistent with *Babesia* were first described by Babès in 1888 in his evaluation of the cause of febrile hemoglobinuria in cattle in Romania.<sup>1-3</sup>

In the past decade, cases of babesiosis in humans have been reported with increasing frequency, especially along the northeastern coast of the United States. The aim of this article is to summarize the current knowledge of this infection and provide guidance to clinicians.

## Pathogenesis

Of the more than 100 species of *Babesia*, *Babesia microti* (in the United States) and *Babesia divergens* and *Babesia bovis* (in Europe) cause most infections in humans. *B. microti* also infects various small mammals and primates, while *B. divergens* has been

found to infect rats and gerbils as well as its main bovine host. Recently, a previously unknown species of *Babesia* (WA-1) was isolated from an immunocompetent man in Washington state who had clinical babesiosis.<sup>4,5</sup> Researchers also described another probable new babesial species (MO1) associated with the first reported case of babesiosis acquired in the state of Missouri. MO1 is probably distinct from *B. divergens* but the two share morphologic, antigenic and genetic characteristics.<sup>6</sup>

Ixodid (or hard-bodied) ticks, in particular *Ixodes dammini* (*Ixodes scapularis*) and *Ixodes ricinus*, are the vectors of the parasite. Ticks ingest *Babesia* while feeding off the host, and the parasite multiplies within the tick's gut wall. The parasites then spread to the tick's salivary glands. Inoculation into a vertebrate host occurs by a tick larva, nymph or adult.<sup>2,3</sup> Infection in humans usually occurs from late spring to early fall.

After an infectious tick bite, the parasites invade red blood cells and a trophozoite differentiates, replicating asexually by budding with the formation of two to four merozoites. A second type of undifferentiated trophozoite is also formed that does not replicate but

*Most cases of babesiosis are tick-borne, but cases of transfusion-associated and transplacental/perinatal transmission have also been reported.*

enlarges and differentiates into gametocyte-like forms similar to that seen in *Plasmodium* species. Merozoites eventually disrupt infected erythrocytes and reinvade other red blood cells.<sup>1-3</sup>

### Epidemiology

Babesiosis has rarely been reported outside the United States. Sporadic cases have been reported from a number of countries including France, the former Yugoslavia, United Kingdom, Ireland, the former Soviet Union and Mexico. In the United States, infections have been reported from many states but the most endemic areas are the islands off the coast of Massachusetts (including Nantucket and Martha's Vineyard) and New York (including eastern and south central Long Island, Shelter Island and Fire Island) and in Connecticut.<sup>1-3,7,8</sup> In these areas, asymptomatic human infection seems to be common.

Between 1968 and 1993, more than 450 *Babesia* infections were confirmed in the United States by blood smears or serologic testing, but the prevalence of babesiosis is difficult to estimate because of lack of surveillance, and because infections are often asymp-

tomatic. A recent study<sup>9</sup> evaluated the seroprevalence and seroconversion for tick-borne diseases in a high-risk population in the northeast United States. In this one-year seroconversion study of patients in New York state who were at high risk for tick-borne diseases, antibodies to *B. microti* were seen in seven of 671 participants (1 percent), including one asymptomatic seroconversion during the year of observation.<sup>9</sup>

Transfusion-associated babesiosis has also been described.<sup>10</sup> The risk factors for the donors have included exposure to endemic areas and being a recipient of blood transfusions. Patients receiving erythrocyte transfusions are at highest risk, while infection after transfusion of plasma has not been reported. In a survey of 779 blood donors in Cape Cod, Mass., seropositivity ranged from 3.3 to 4.9 percent, which was comparable with that in Boston, a nonendemic area.<sup>11</sup>

Overall, the risk of acquiring babesiosis from a blood transfusion is very low. In Connecticut, the risk of acquiring babesiosis from a transfused unit of packed red blood cells was estimated at about 0.17 percent (95 percent CI, 0.004 to 0.9 percent) and was even lower from a transfused unit of platelets (95 percent CI, 0.0 to 0.8 percent).<sup>12</sup> Finally, transplacental/perinatal transmission has been reported.<sup>2,3</sup>

### Clinical Features

Babesiosis in the United States has varied substantially from that described in Europe. To date, most of the patients described in Europe have been asplenic, have presented with acute febrile hemolytic disease and their clinical courses have almost always been fatal.<sup>2,3</sup>

In the United States, the clinical spectrum of the infection ranges from asymptomatic to rapidly progressive and fatal. Although babesiosis can affect persons of all ages, most patients present in their 40s or 50s. After a recognized tick bite, the incubation period of babesiosis varies from five to 33 days.<sup>1,3,7</sup>

---

### The Author

ELEFThERIOS MYLONAKIS, M.D., is a clinical and research fellow in infectious diseases at Massachusetts General Hospital, Harvard Medical School, Boston, and the recipient of a research fellowship for physicians from the Howard Hughes Medical Institute, Chevy Chase, Md. Dr. Mylonakis earned a doctorate degree in infectious diseases and internal medicine at the National University of Athens Faculty of Medicine and School of Health Sciences. He also completed a residency and chief medical residency in internal medicine at Miriam Hospital, Brown University School of Medicine, Providence, RI.

*Address correspondence to Eleftherios Mylonakis, M.D., Infectious Diseases Division, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114 (e-mail: emylonakis@partners.org). Reprints are not available from the author.*

**TABLE 1**  
**Common Presenting Signs**  
**and Symptoms of Human Babesiosis**

---

Generalized weakness
Fever
Gastrointestinal symptoms (anorexia, nausea, abdominal pain, vomiting, diarrhea, etc.)
Headache
Myalgia
Weight loss
Arthralgia
Respiratory symptoms (cough, shortness of breath, etc.)
Dark urine

---

However, most patients do not recall recent tick exposure. After an infected blood transfusion, the incubation period can be up to nine weeks.<sup>2,3,7,8</sup>

Both humoral and cell-mediated immune mechanisms influence the outcome of the infection. Factors associated with more severe disease include advanced age, previous splenectomy and immunodeficiency states including acquired immunodeficiency syndrome.<sup>7,13,14</sup>

Symptoms include high fever (up to 40°C [104°F]), chills, diaphoresis, weakness, fatigue, anorexia and headache (*Table 1*). Later in the course of the illness, the patient may develop jaundice and dark urine. Physical examination may reveal hepatomegaly and splenomegaly or evidence of shock. Rash is an uncommon symptom in babesiosis.<sup>1,2,3,7</sup> Signs of central nervous system involvement include headache, photophobia, neck and back stiffness, altered sensorium and emotional lability.<sup>3,7,15</sup>

Congestive heart failure, disseminated intravascular coagulation and acute respiratory distress syndrome (that can occur even a few days after the onset of effective antimicrobial treatment) are the most common complications of human babesiosis (*Table 2*). Renal failure and myocardial infarction also have

been associated with severe babesiosis. Researchers reviewed the clinical data and prognostic factors among 139 hospitalized cases in New York state between 1982 and 1993.<sup>16</sup> Nine patients (6.5 percent) died, one fourth of the patients were admitted to the intensive care unit and one fourth of the patients required hospitalization for more than 14 days. The most common symptoms were fatigue/malaise/weakness (91 percent), fever (91 percent), shaking chills (77 percent) and diaphoresis (69 percent). Fifty-two percent of patients had a history of chronic disease. On average, a 12- to 14-day delay was noted between onset of symptoms and initiation of appropriate antibiotic treatment. Alkaline phosphatase levels greater than 125 U per L, white blood cell counts greater than  $5 \times 10^9$  per L, history of cardiac abnormality, history of splenectomy, presence of heart murmur and parasitemia values of 4 percent or higher were associated with disease severity.<sup>16</sup>

### Diagnosis

Mild to severe hemolytic anemia and a normal to slightly depressed leukocyte count are common nonspecific findings in babesiosis. Usually, the diagnosis is based on typical morphologic picture on the blood smear in conjunction with epidemiologic information. A Wright- or Giemsa-stained peripheral blood smear is most commonly used to demonstrate the presence of intraerythro-

**TABLE 2**  
**Common Complications**  
**of Human Babesiosis**

---

Acute respiratory distress syndrome
Anemia requiring transfusion
Congestive heart failure
Disseminated intravascular coagulation
Hypotension/shock
Myocardial infarction
Renal failure

---

cytic parasites (Figure 1). Rarely, tetrads of merozoites are visible.

The organisms are intraerythrocytic ring forms closely resembling Plasmodium, the organism causing malaria. Three distinguishing features differentiate the two organisms. Babesial organisms usually form tetrads ("Maltese cross"), do not have hemozoin pigments within the affected red blood cells and have extracellular merozoites.<sup>17,18</sup>

Serologic evaluation with the indirect immunofluorescent antibody test with use of *B. microti* antigen is available in a few laboratories. The cutoff titer for determination of a positive result varies with the particular laboratory protocol used, but in most laboratories, titers of more than 1:64 are considered consistent with *B. microti* infection. Tenfold to 20-fold higher titers can be observed in the acute setting, with a gradual decline over weeks to months. The correlation between the level of the titer and the severity of symptoms is poor.<sup>1-3</sup>

Detection of *B. microti* by polymerase chain reaction (PCR) was first described in 1992.<sup>19</sup> A more recent study,<sup>20</sup> in which PCR was used prospectively for diagnosing sus-

pected cases in the northeastern United States has shown that PCR is more sensitive and equally specific for the diagnosis of acute cases, in comparison with direct smear examination and hamster inoculation. PCR-based methods may also be indicated for monitoring of the infection.<sup>20</sup>

### Treatment

Babesiosis may continue for more than two months after treatment and when left untreated, silent babesial infection may persist for months or even years. Researchers<sup>21</sup> compared the duration of parasitemia in persons who had received specific antibabesial therapy with that in silently infected persons who had not been treated. Babesial DNA persisted for 16 days in 22 acutely ill subjects who received clindamycin and quinine therapy ( $P = 0.03$ ). Among the subjects who did not receive specific therapy, symptoms of babesiosis persisted up to 114 days.<sup>21</sup>

Treatment with the combination of quinine (Quinamm; 650 mg of salt orally, three times daily) and clindamycin (Cleocin; 600 mg orally, three times daily, or 1.2 g parenterally, twice daily) for seven to 10 days is the most commonly used treatment. The pediatric dosage is 20 to 40 mg per kg per day for quinine and 25 mg per kg per day for clindamycin. The fortuitous discovery of this regimen for babesiosis in humans was made during the management of a patient with presumed transfusion-acquired malarial infection. The patient was initially treated with chloroquine (Aralen Injection); however, because of lack of response, treatment was changed to quinine and clindamycin.<sup>2,3,22,23</sup>

Several other drugs have been evaluated, including tetracycline, primaquine, sulfadiazine (Microsulfon) and pyrimethamine (Fansidar). Results have varied. Pentamidine (Pentam) has proved to be moderately effective in diminishing symptoms and decreasing parasitemia.

Atovaquone suspension (Mepron; 750 mg twice daily) plus azithromycin (Zithromax;

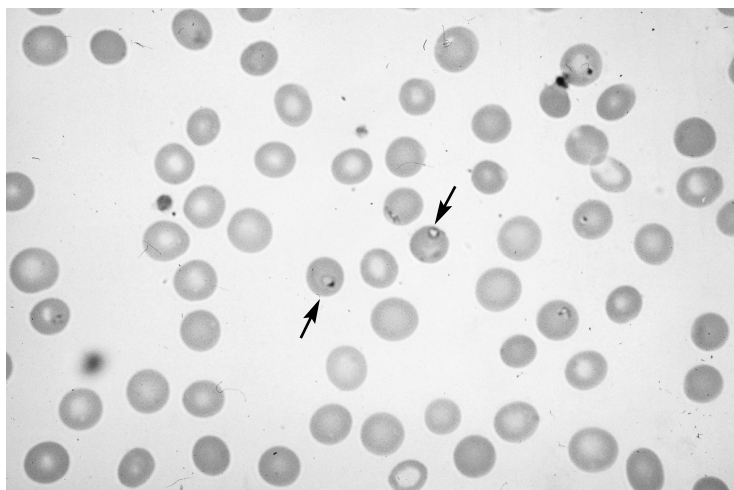


FIGURE 1. Human erythrocytes showing infection with *Babesia microti*. Note that the ring forms with a central pale area inside the red blood cell (arrows).

500 to 1,000 mg per day) is a very effective treatment. This treatment was found to be effective for the prevention and treatment of babesiosis in hamsters. Clindamycin plus quinine was also effective but less so than atovaquone. When treatment was not started until parasitemia became established, atovaquone in dosages of 300, 150 and 80 mg per kg per day was effective in the recovery of all animals compared with 50 percent of those receiving 10 mg per kg per day and 10 percent of untreated control subjects.<sup>24</sup> Of note is that, in the same model, when atovaquone was used as monotherapy, the disease recurred. Organisms obtained from these animals, when inoculated into uninfected animals, proved to be unresponsive to atovaquone therapy, suggesting the emergence of drug resistance. Resistant organisms did not emerge in hamsters treated with the combination of atovaquone and azithromycin.<sup>25</sup>

In humans, a prospective, randomized study<sup>26</sup> comparing the efficacy of clindamycin and quinine with that of atovaquone and azithromycin has been conducted. This study included 58 patients with non-life-threatening babesiosis. Forty received atovaquone and azithromycin and 18 received clindamycin and quinine. The resolution of symptoms and parasitemia were similar between the two groups and both treatments were effective for all patients. However, 72 percent of the patients who received quinine and clindamycin suffered side effects from the antibiotics, compared with 15 percent of patients in the atovaquone and azithromycin group.<sup>26</sup>

Exchange transfusion, together with antibabesial chemotherapy, may be necessary in critically ill patients. This treatment is usually reserved for patients who are extremely ill—with blood parasitemia of more than 10 percent, massive hemolysis and asplenia.<sup>17</sup>

### Prevention

Prevention of babesiosis involves avoiding endemic regions during the peak transmission months of May through September. This rec-

ommendation may be especially relevant for asplenic or immunocompromised persons in whom babesiosis can be a devastating illness.<sup>1,2</sup> Using insect repellent is advised during outdoor activities, especially in wooded or grassy areas. One of the most effective tick repellents is *N,N*-diethyl-*m*-toluamide (DEET). It is commercially available in concentrations up to 100 percent. However, serious toxic and allergic reactions have been reported in persons who have used it frequently or in high concentrations. In young children, toxic encephalopathy has occurred.<sup>2,3</sup> Products with 10 to 35 percent DEET will provide adequate protection under most conditions.

Early removal of ticks is important; the tick must remain attached for at least 24 hours before the transmission of *B. microti* occurs. Therefore, daily self-examination is recommended for persons who engage in outdoor activities in endemic areas. Pets also must be examined for ticks because they may carry ticks into the home.

### Co-infection with Other Species of Tick-Transmitted Diseases

Co-infection with *Borrelia burgdorferi* and *B. microti* may be relatively common in endemic areas of the northeastern and upper midwestern United States. Approximately 10 percent of patients with Lyme disease in southern New England are co-infected with babesiosis in sites where both diseases are zoonotic. The number of symptoms and duration of illness in patients with concurrent Lyme disease and babesiosis are greater than in patients with either infection alone.<sup>27,28</sup>

Co-infection with Ehrlichia species may also be seen. Three species of Ehrlichia have been described that infect humans, *Ehrlichia chaffeensis*, *Ehrlichia phagocytophila* and *Ehrlichia ewingii*. Typically, patients have a nonspecific febrile illness. Rash is uncommon with human granulocytic ehrlichiosis but common with human monocytic ehrlichiosis. Laboratory findings often include leukopenia, thrombocytopenia and increases in serum

hepatic enzyme activities. In areas endemic for Lyme disease and ehrlichiosis, it may be advisable to add doxycycline (Vibramycin), 100 mg twice a day by mouth, in the management of patients with babesiosis until serologic confirmation has been made.

*The author is the recipient of a research fellowship for physicians from the Howard Hughes Medical Institute, Chevy Chase, Md.*

REFERENCES

1. Gelfand JA. Babesia. In: Mandell GL, Douglas RG, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and practice of infectious diseases*. 5th ed. New York: Churchill Livingstone, 2000;2899-902.
2. Boustani MR, Gelfand JA. Babesiosis. *Clin Infect Dis* 1996;22:611-5.
3. Pruthi RK, Marshall WF, Wiltsie JC, Persing DH. Human babesiosis. *Mayo Clin Proc* 1995;70:853-62.
4. Persing DH, Herwaldt BL, Glaser C, Lane RS, Thomford JW, Mathiesen D, et al. Infection with a babesia-like organism in northern California. *N Engl J Med* 1995;332:298-303.
5. Quick RE, Herwaldt BL, Thomford JW, Garnett ME, Eberhard ML, Wilson M, et al. Babesiosis in Washington State: a new species of Babesia? *Ann Intern Med* 1993;119:284-90.
6. Herwaldt B, Persing DH, Precigout EA, Goff WL, Mathiesen DA, Taylor PW, et al. A fatal case of babesiosis in Missouri: identification of another piroplasm that infects humans. *Ann Intern Med* 1996;124:643-50.
7. Spach DH, Liles WC, Campbell GL, Quick RE, Anderson DE, Fritsche TR. Tick-borne diseases in the United States. *N Engl J Med* 1993;329:936-47.
8. Spielman A, Wilson ML, Levine JF, Piesman J. Ecology of Ixodes dammini-borne human babesiosis and Lyme disease. *Annu Rev Entomol* 1985;30:439-60.
9. Hilton E, DeVoti J, Benach JL, Halluska ML, White DJ, Paxton H, et al. Seroprevalence and seroconversion for tick-borne diseases in a high-risk population in the northeast United States. *Am J Med* 1999;106:404-9.
10. Dobroszycki J, Herwaldt BL, Boctor F, Miller JR, Linden J, Eberhard ML, et al. A cluster of transfusion-associated babesiosis cases traced to a single asymptomatic donor. *JAMA* 1999;281:927-30.
11. Popovsky MA, Lindberg LE, Syrek AL, Page PL. Prevalence of Babesia antibody in a selected blood donor population. *Transfusion* 1988;28:59-61.
12. Gerber MA, Shapiro ED, Krause PJ, Cable RG, Badon SJ, Ryan RW. The risk of acquiring Lyme disease or babesiosis from a blood transfusion. *J Infect Dis* 1994;170:231-4.
13. Benezra D, Brown AE, Polsky B, Gold JW, Armstrong D. Babesiosis and infection with human immunodeficiency virus (HIV) [Letter]. *Ann Intern Med* 1987;107:944.
14. Rosner F, Zarrabi MH, Benach JL, Habicht GS. Babesiosis in splenectomized adults. Review of 22 reported cases. *Am J Med* 1984;76:696-701.
15. Ruebush TK 2d, Cassaday PB, Marsh HJ, Lisker SA, Voorhees DB, Mahoney EB, et al. Human babesiosis on Nantucket Island. Clinical features. *Ann Intern Med* 1977;86:6-9.
16. White DJ, Talarico J, Chang HG, Birkhead GS, Heimberger T, Morse DL. Human babesiosis in New York State: Review of 139 hospitalized cases and analysis of prognostic factors. *Arch Intern Med* 1998;158:2149-54.
17. Bonoan JT, Johnson DH, Cunha BA. Life-threatening babesiosis in an asplenic patient treated with exchange transfusion, azithromycin, and atovaquone. *Heart Lung* 1998;27:424-8.
18. Loutan L, Rossier J, Zufferey G, Cuenod D, Hatz C, Marti HP, Gern L. Imported babesiosis diagnosed as malaria [Letter]. *Lancet* 1993;342:749.
19. Persing DH, Mathiesen D, Marshall WF, Telford SR, Spielman A, Thomford JW, et al. Detection of Babesia microti by polymerase chain reaction. *J Clin Microbiol* 1992;30:2097-103.
20. Eskow ES, Krause PJ, Spielman A, Freeman K, Aslanzadeh J. Southern extension of the range of human babesiosis in the eastern United States. *J Clin Microbiol* 1999;37:2051-2.
21. Krause PJ, Spielman A, Telford SR 3rd, Sikand VK, McKay K, Christianson D, et al. Persistent parasitemia after acute babesiosis. *N Engl J Med* 1998;339:160-5.
22. Rowin KS, Tanowitz HB, Wittner M. Therapy of experimental babesiosis. *Ann Intern Med* 1982;97:556-8.
23. Wittner M, Rowin KS, Tanowitz HB, Hobbs JF, Saltzman S, Wenz B, et al. Successful chemotherapy of transfusion babesiosis. *Ann Intern Med* 1982;96:601-4.
24. Weiss LM, Wittner M, Wasserman S, Oz HS, Retsema J, Tanowitz HB. Efficacy of azithromycin for treating Babesia microti infection in the hamster model. *J Infect Dis* 1993;168:1289-92.
25. Wittner M, Lederman J, Tanowitz HB, Rosenbaum GS, Weiss LM. Atovaquone in the treatment of Babesia microti infections in hamsters. *Am J Trop Med Hyg* 1996;55:219-22.
26. Krause PJ, Lepore T, Sikand VK, Gadbow JJ, Burke G, Telford SR, et al. Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000;343:1454-8.
27. Krause PJ, Telford SR 3rd, Spielman A, Sikand V, Ryan R, Christianson D, et al. Concurrent Lyme disease and babesiosis. Evidence for increased severity and duration of illness. *JAMA* 1996;275:1657-60.
28. Sweeney CJ, Ghassemi M, Agger WA, Persing DH. Coinfection with Babesia microti and Borrelia burgdorferi in a western Wisconsin resident. *Mayo Clin Proc* 1998;73:338-41.