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Babesiosis

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Summary

Babesiosis is a worldwide tick-borne zoonosis caused by hemoprotozoan parasites of the genus Babesia. *Babesia microti* is the main etiologic agent of human babesiosis and is endemic in the northeastern and the upper Midwestern United States. The geographic expansion of babesiosis has followed that of Lyme disease, but has remained more restricted. The emergence of human babesiosis poses a serious health threat in highly endemic areas. Fever is the salient feature of babesiosis and often is accompanied by a series of non-specific symptoms, explaining why diagnosis may be delayed or missed. The diagnosis is confirmed by identification of babesia organisms on Giemsa stained blood smears, detection of babesia DNA by PCR, or a four-fold rise in anti-babesia antibody titers in acute and convalescent sera. The disease may be severe or fatal, particularly in patients who are otherwise healthy but older than 50 years of age, and in patients who are immunocompromised regardless of age. Most patients have complete recovery following a standard 7 to 10 day course of antimicrobial therapy.

Keywords

babesiosis; *Babesia microti*; protozoan; Apicomplexa; erythrocyte; tick; transfusion

Introduction

Babesiosis is caused by intraerythrocytic protozoan parasites that are transmitted by ticks, or less commonly through blood transfusion or transplacentally. The microorganisms that we now recognize as babesia were first described by Babes in 1888 when he investigated the cause of hemoglobinuria in febrile cattle. Five years later, Smith and Kilbourne identified a tick as the vector for *Babesia bigemina* that caused Texas cattle fever, thereby establishing for the first time transmission of an infectious agent by an arthropod vector. Human babesiosis was first recognized in a splenectomized patient in Europe but most cases have been reported from the northeastern and upper midwestern United States in people with an intact spleen and no history of immune impairment.[1-3] Cases are sporadically reported in Asia, Africa, Australia, Europe, and South America. Babesiosis shares many clinical features with malaria and can be fatal, particularly in the elderly and the immunocompromised.

Epidemiology

The pathogens

Babesia species belong to the phylum Apicomplexa that is comprised of several important human pathogens such as species of Plasmodium, Toxoplasma, and Cryptosporidium. Of the large number of babesia species that infect wild and domestic animals, only a few are known to cause disease in humans, including *Babesia microti and B. microti-like, Babesia duncani* and *B. duncani*-type organisms, *Babesia divergens* and *B. divergens*–like organisms, *Babesia venatorum,* and KO1.[2,4] The genome of *B. microti* recently has been sequenced. [5-6] Phylogenetic analyses indicate that *B. microti* is a species complex that is distant from all species of Babesidae and Theileridae and constitutes a new genus in the Apicomplexa phylum.[5-6] *B. microti* has the smallest genome among all Apicomplexan parasites sequenced to date with ∼3,600 genes distributed on four nuclear chromosomes, one mitochondrial chromosome and one apicoplast chromosome. These genomic efforts have helped gain further understanding about the biology and phylogenetics of the parasite and have identified several targets for the development of novel therapies for human babesiosis.

Transmission

Ixodes ticks are the primary mode of transmission of babesia species to vertebrates, including humans (Figure 1). Babesia species are maintained in a wide range of vertebrate reservoirs; humans are incidental and terminal hosts. The primary reservoir for *B. microti* in the northeastern and upper Midwestern United States is the white-footed mouse (*Peromyscus leucopus*), but the parasite also has been found in shrews, chipmunks, voles, and rats.[4] The primary vector is *Ixodes scapularis*, which also transmits *Borrelia burgdorferi,* the etiologic agent of Lyme disease, *Anaplasma phagocytophilum*, *Borrelia miyamotoi*, *Ehrlichia muris*-like agent, and Powassan virus.[4,7] Humans can be infected with two or more of these pathogens. The prevalence of *B. microti* infection in nymphal *I. scapularis* ticks ranges from 1% in newly endemic areas to 20% in some well-established endemic areas.[7] Initially identified on the coastal islands of southern New England, *B. microti* has spread north, west, and south to encompass much of the northeastern United

States. This geographic expansion mimics that of Lyme disease but has proceeded more slowly. The reported incidence of babesiosis is lower than that of Lyme disease due to a more restricted geographic range, lower tick infection rate, greater proportion of asymptomatic infection, insufficient physician awareness, and greater difficulty in diagnosis [2,7] Carefully designed epidemiologic studies have shown that differences in the incidence of babesiosis and Lyme disease are small at certain sites that have long been endemic for both diseases.[7-8]

Each of the three active stages in the life cycle of *I. scapularis* (larva, nymph, and adult) takes a blood meal from a vertebrate host to mature to the next stage (Figure 1).[2,4] The tick transmission cycle begins in late summer when newly hatched larvae ingest the parasite during a blood meal obtained from an infected host. *B. microti* eventually cross the tick gut epithelium to reach the hemolymph and travel to the salivary glands. The parasites remain dormant sporoblasts when larvae molt into nymphs. Upon attachment of a *B. microti* infected nymphal tick to a vertebrate host, sporozoites are produced and released into the dermis of the host within tick saliva. Nymphs transmit *B. microti* sporozoites to vertebrate hosts in late spring and early summer of the following year.[4] Once fed, nymphs molt into adults in late summer and early fall. Adults feed on the white-tailed deer (*Odocoileus virginianus*), which is an important host for survival of the adult tick but is not a reservoir for *B. microti*.[4] Larvae, nymphs, and adults all feed on humans, but the nymph is the primary vector because of its summer questing activity and its small size. *B. microti* transmission from *I. scapularis* to vertebrate hosts requires 36 to 72 hours because sporozoites are not readily available in the salivary glands and are generated following activation of dormant sporoblasts upon tick exposure to warm blooded hosts.[9] The continuous expansion of the deer population is thought to be a major factor in the increased density of *I. scapularis* and increased incidence of human babesiosis.[4]

Babesiosis also may be acquired through blood transfusion and transplacental transmission. More than 170 transfusion-transmitted cases have been reported.[10-11] *B. microti* is the most common transfusion-transmitted pathogen reported in the United States. Although most cases occur during or shortly after summer in highly endemic areas, transfusion-transmitted babesiosis also occurs year round and in non-endemic areas. About a fifth of the cases acquired through blood transfusion have had a fatal outcome.[10-11] Most cases of babesiosis in neonates have been acquired through blood transfusion whereas at least one case has been acquired by transplacental transmission.[2,12,13]

Human epidemiology

The incidence of human babesiosis has exponentially increased in the United States over the past five decades.[8,14-16] Most cases occur in seven states, five of which are located in the Northeast (MA, CT, RI, NY, NJ) and two in the upper Midwest (MN, WI). The geographic range of human babesiosis has expanded beyond these highly endemic areas, and cases of human babesiosis caused by *B. microti* are now reported all along the northeastern seaboard and inland, ranging from Maine to Maryland (Figure 2).[2,14-17] Most cases of human babesiosis occur in the summer and in areas where the tick vector, vertebrate reservoirs, and deer are in close proximity to humans. At some sites and in certain years of high

transmission, babesiosis may impose a significant public health burden.[8] Cases caused by *B. duncani* or *B. duncani*-type organisms have been sporadic on the Pacific Coast from northern California to Washington State. Three cases due to *B. divergens*-like organisms have been documented in Missouri, Kentucky, and Washington State.

Cases of human babesiosis have been reported throughout the world. *B. divergens* is the most common cause of babesiosis in Europe where a few cases of *B. microti* and *B. venatorum* infections also have been described. Human cases have been reported in Africa, Asia, Australia and South America.[2]

Clinical Manifestations

Asymptomatic infection

Asymptomatic *B. microti* infection has been recorded in about a fifth of adults and half of children in a decade long cohort study on Block Island, Rhode Island, a highly endemic area.[8] Serosurveys in other highly endemic areas have confirmed the prevalence of asymptomatic infection as shown by the disparity between seroprevalence rates and the number of reported cases of babesiosis.[8,11,15] In New England, seroprevalence has varied between 0.5% and 16%.[11,15]

Mild to moderate illness

Clinical manifestations of babesiosis range from mild to fulminating illness resulting in death. Following an incubation period of about 1 to 4 weeks after a tick bite or 1 to 9 weeks (but up to 6 months) following transfusion of contaminated blood products, a gradual onset of malaise and fatigue is accompanied by fever and one or more of the following: chills, sweats, anorexia, headache, myalgia, nausea, nonproductive cough and arthralgia (Table 1).[14,16-23] Also reported are emotional liability and depression, hyperesthesia, sore throat, abdominal pain, vomiting, conjunctival injection, photophobia, and weight loss.

Fever is the salient feature on physical examination, but splenomegaly and hepatomegaly occasionally are noted. Less common are mild pharyngeal erythema, jaundice, and retinopathy with splinter hemorrhages and retinal infarcts.[14,16,19-22] Rash seldom is noted and if present should raise the possibility of concurrent Lyme disease. Laboratory abnormalities that reflect the hemolytic anemia caused by invasion and lysis of red blood cells by babesia organisms include low hemoglobin, low hematocrit and elevated lactic dehydrogenase.[14,16,19,22] Serum liver enzyme concentrations often are elevated. The leukocyte count is variable. Thrombocytopenia is common.[16] Elevated serum levels of blood urea nitrogen and creatinine may occur, especially in severe illness and often are accompanied by proteinuria. Symptoms usually resolve in a week or two but anemia and fatigue may persist for several months.[19,24] Parasitemia (as measured by parasite DNA) has been detected for more than a year even after resolution of symptoms and completion of treatment.[24]

Severe disease

Some patients, especially those who are older than 50 years, are immunocompromised, have comorbidities, or experience *B. divergens* infection may experience severe babesiosis that requires hospital admission. Complications include adult respiratory distress syndrome, pulmonary edema, disseminated intravascular coagulation, congestive heart failure, renal failure, coma, splenic rupture, or a prolonged relapsing course of illness despite standard antibiotic therapy.[14,16,22-23,25] Death occurs in up to a tenth of patients hospitalized for *B. microti* infection.[16,22] The fatality rate is even higher among those who are immunocompromised or acquired the infection through blood transfusion.[2-3,22,25] Concurrent infection with *B. microti* and one or several tick-transmitted pathogens can occur and may increase the number and duration of acute symptoms.[26]

Pathogenesis

Red cell invasion and lysis

After attachment and entry into the erythrocyte, babesia organisms mature into trophozoites that eventually undergo asexual budding to yield two or four daughter cells known as merozoites. Released into the bloodstream, free merozoites quickly invade nearby red blood cells to ensure persistence of the infection in the host.

Erythrocyte lysis is associated with many of the clinical manifestations and complications of babesiosis, including fever, anemia, jaundice, hemoglobinemia, hemoglobinuria, and renal insufficiency. The absence of synchrony in asexual reproduction of the parasite may explain the lack of massive hemolysis associated with babesiosis and therefore the milder clinical presentation of babesiosis when compared with malaria.

Host immune response

The pathogenesis of babesia infection is closely linked to the host response, and studies of babesiosis in animal models suggest that disease results from the excessive production of proinflammatory cytokines.[27-28] The release of proinflammatory cytokines may be initiated by contact of immune cells with the glycosylphosphatidylinositol (GPI) anchors of babesia proteins expressed at the surface of the parasite or the surface of infected red blood cells.[5] Proinflammatory cytokines subsequently stimulate production of downstream mediators, such as nitric oxide, which may kill parasites, but also cause cellular damage when produced in excess. Obstruction of blood vessels due to adherence of parasitized erythrocytes to vascular endothelium with ensuing tissue ischemia and necrosis has been hypothesized to contribute to pathology.[28] Although cytoadherence occurs in cattle infected with *Babesia bovis*, it has not been observed in human babesiosis.[29]

The immune response in babesiosis involves macrophages and their products, such as tumor necrosis factor-α and interleukin-12, B-lymphocytes and antibody secretion, T lymphocytes and cytokine production such interferon-γ, and complement factors.[2, 27-28, 30] Most fatal cases of human babesiosis occur in splenectomized individuals, although asplenia does not always result in death or even severe illness. The spleen plays a critical role in protection against Babesia spp. because resident phagocytes and histiocytes ingest and clear infected

red blood cells. Given that anemia often is more severe than predicted by parasitemia, uninfected red blood cells likely are removed. Whether caused by hemolysis of infected red blood cells or by non-specific removal of uninfected red blood cells, the anemia of babesiosis elicits stress-induced erythropoiesis and reticulocytosis. The splenic immune response and the extramedullary erythropoiesis explain why patients who experience high-grade parasitemia tend to present with splenomegaly.

Aging is an important risk factor for severe babesiosis. Most clinically apparent cases are reported in adults, although seroprevalence studies indicate that children are equally exposed to *Babesia* infected ticks. Most severe cases of babesiosis occur in people over 50 years of age even if otherwise healthy[16] Almost all of the pediatric cases reported have been in neonates and caused by transfusion of blood products.[23,31] Data from a murine model of human babesiosis suggest that resistance to *B. microti* infection conferred by the adaptive immune system is genetically determined and altered by aging.[31-32] Sterile immunity may be slow to develop as parasite DNA (a marker of parasitemia) may persist for months to years after recovery from the initial illness.[20]

Diagnosis

Clinical diagnosis

The diagnosis of babesiosis is based on epidemiological and medical history, physical examination, and confirmatory laboratory tests (Figure 3).[2] A diagnosis of babesiosis should be considered when a patient has a history of travel to or residence in a babesia endemic area or has received a blood transfusion in the previous six months and presents with symptoms that are consistent with babesiosis. A history of tick exposure is useful but may be absent as the bite often is unnoticed.

Laboratory diagnosis

The diagnosis of babesiosis is confirmed by laboratory testing, most commonly by identification of the organism on Giemsa or Wright stained thin blood smears (Figure 1).[33] Trophozoites of *Babesia* spp. are round, oval or pear-shaped and have a blue cytoplasm with a red chromatin. Ring forms are most common and may resemble the rings of early stage *Plasmodium falciparum* trophozoites. Babesia are distinguished from Plasmodia by the absence of hemozoin deposit in the ring form, the lack of banana-shaped gametocytes, and the presence of tetrads (Maltese cross).[2] Multiple thin blood smears should be examined in the early stage of the illness, as parasitemia often is low at presentation.

PCR is a more sensitive test for *B. microti* infection than blood smear and provides a molecular characterization of the babesia species.[33] The advent of real-time PCR has considerably lowered the limit of detection. [34-36] Endpoint *B. microti* PCR has been widely available for about two decades whereas real-time *B. microti* PCR has recently been developed and is now available from several commercial diagnostic laboratories. The diagnosis also can be confirmed and the organism amplified for genetic sequencing by injecting patient blood into small laboratory animals, although this approach is less sensitive and more time-consuming and costly than PCR.[33]

Serology is useful for supporting or confirming the diagnosis. A four-fold rise in babesia IgG titer in acute and convalescent sera confirms recent infection whereas a single positive antibody titer is not confirmatory as it cannot distinguish recent from past infection. The indirect immunofluorescence assay (IFA) is the most common babesia serologic test. Others include ELISA and western blot.[37-38] The antigen used in babesia antibody testing should be specific for the babesia species that is locally prevalent. For example, *B. duncani* antibody testing would not be informative in areas where *B. microti* is endemic and *B. duncani* absent. Furthermore, the antibody titer that defines the threshold for a positive serology often differs from one babesia species antibody assay to another and occasionally from one laboratory to another for the same babesia species. Babesia antibody testing is of limited use in fulminant infection such as *B. divergens* illness because initial antibody testing often is negative. During the acute phase of the illness, *B. microti* IgG titers usually exceed 1:1024, but typically decline to 1:64 or less within 8 to 12 months.[24] A positive serology for *B. divergens* does not exclude *B. venatorum* infection as antibodies against *B. divergens* antigen cross-react with *B. venatorum* antigen. Cases of *B. duncani* infection have been too few to validate the IFA for this pathogen.

Treatment

Asymptomatic infection

A one-week course of atovaquone plus azithromycin should be considered for any person identified with asymptomatic babesial infection (as determined by blood smear or PCR) for longer than three months.[24,39-40] People who have a positive serology but in whom parasites cannot be detected by blood smears and by PCR should not be treated, as they likely have resolved the infection.

Mild to moderate illness

The recommended treatment for mild to moderate babesiosis consists of atovaquone plus azithromycin for 7 to 10 days (Table 2).[18,40] This regimen was compared with clindamycin plus quinine in the only prospective trial of antibabesial therapy in humans.[15] Both drug combinations were equally effective in clearing symptoms and parasitemia. Adverse effects were reported in 15 percent of subjects who received atovaquone plus azithromycin compared with 72 percent of subjects who received clindamycin plus quinine. Drug reactions were so severe that treatment had to be stopped or drug dosage decreased in approximately one third of subjects who took clindamycin plus quinine but in only 2 percent of subjects who received atovaquone plus azithromycin. Although rare cases of resistance to atovaquone plus azithromycin have been reported, this combination has been proven effective in the vast majority of children and adults.[18,40]

Severe disease

Severe disease typically develops in patients who have one or more of the following risk factors: age >50 years, splenectomy, malignancy, HIV infection, or immunosuppressive therapy. Clindamycin plus quinine is the combination of choice for these patients because of cumulative experience with this combination for severe disease.[23,40] Oral quinine can be

replaced with intravenous quinidine, but a patient treated with intravenous quinine or quinidine must be closely monitored in a hospital setting for possible Q-T prolongation.

Persistent or relapsing babesiosis despite a standard course of antimicrobial therapy has occurred in patients who present with two or more of the risk factors listed above. In these patients, resolution of infection may require at least 6 weeks of antimicrobial therapy, including 2 weeks after babesia parasites are no longer detected on blood smears.[25] In addition to clindamycin plus quinine, several antibiotic combinations have been reported to be effective in a few highly immunocompromised patients. These alternative regimens have consisted of atovaquone-proguanil; atovaquone, clindamycin, plus doxycycline; atovaquone, azithromycin, plus doxycycline; artemisinin, atovaquone, plus doxycycline; atovaquone, azithromycin, plus clindamycin; and azithromycin plus quinine.[24] Close clinical follow-up with repeat blood smears, babesia PCR, and complete blood counts should be performed immediately if symptoms recur.

Partial or complete red blood cell exchange transfusion is recommended for patients with parasitemia 10%, severe anemia (hemoglobin <10 g/dL), or pulmonary, liver or renal impairment. Exchange transfusion rapidly decreases parasitemia, corrects anemia, and removes toxic byproducts of babesia infections.[2,41] Exchange transfusion and treatment with clindamycin plus quinine also is recommended for any patient infected with *B. divergens* because the illness often is fulminant. A combination of intravenous pentamidine plus oral trimethoprim-sulfamethoxazole was effective in treating a case of *B. divergens* infection.[42]

Prevention

Babesiosis can be prevented by avoiding areas where ticks, deer, and mice are known to thrive. It is especially important for asplenic individuals and other immunocompromised patients who are at risk of severe babesiosis, and who live or travel in endemic areas, to avoid tall grass, brush, and forested areas where *I. scapularis* ticks may abound. Use of protective clothing that is sprayed or impregnated with diethyltoluamide (DEET), dimethyl phthalate, or permethrin is recommended for individuals who travel into the foliage of endemic areas.[43-44] A search for ticks should be carried out and the ticks removed as soon as possible.[44-45] Embedded ticks are best removed by use of tweezers to grasp the mouth parts without squeezing the body of the tick.

Landscape-management approaches such as keeping grass mowed, clearing leaf litter, and spraying property with acaricides where tick density is high may help reduce the risk of infection. The risk of Lyme disease and presumably other tick borne diseases can be decreased by limiting the amount of edge between lawn and shrub on private properties.[43,46] Acaricide application to deer using a 4-poster device decreases the number of *I. scapularis* ticks.[47] Reduction in the number of deer on several islands has decreased both the number of *I. scapularis* ticks and the incidence of Lyme disease.[48-49]

Prospective blood donors who have had a history of babesiosis are permanently deferred from donating. There is no FDA approved test for screening of the blood supply for *B. microti*, but some states in highly endemic regions have instituted screening that combines serology and PCR.[50-51]

Although *B. bovis* and *B. bigemina* vaccines are available for use in cattle, no human babesiosis vaccine has been developed.

Exchange transfusion

Partial or complete exchange transfusion should be considered for treatment of severe cases of babesiosis. Exchange transfusion is recommended for any patient who is infected with *B. divergens*.

Acknowledgments

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Key points

- Human babesiosis is an emerging infectious disease caused by hemoprotozoan parasites that are transmitted by tick vectors and less frequently through blood transfusion or transplacentally.

- *Babesia microti*, the most frequent cause of human babesiosis, is endemic in the northeastern and upper midwestern United States and is sporadic throughout the rest of the world.

- Clinical manifestations consist most commonly of a viral-like illness but range from asymptomatic infection to severe illness resulting in complications or death.

- Diagnosis is confirmed by identification of babesia organisms on blood smear, detection of babesia DNA by PCR, or a four-fold rise in babesia antibody titers in acute and convalescent sera.

- Treatment with atovaquone plus azithromycin is used for mild to moderate babesiosis whereas clindamycin plus quinine is recommended for severe disease.
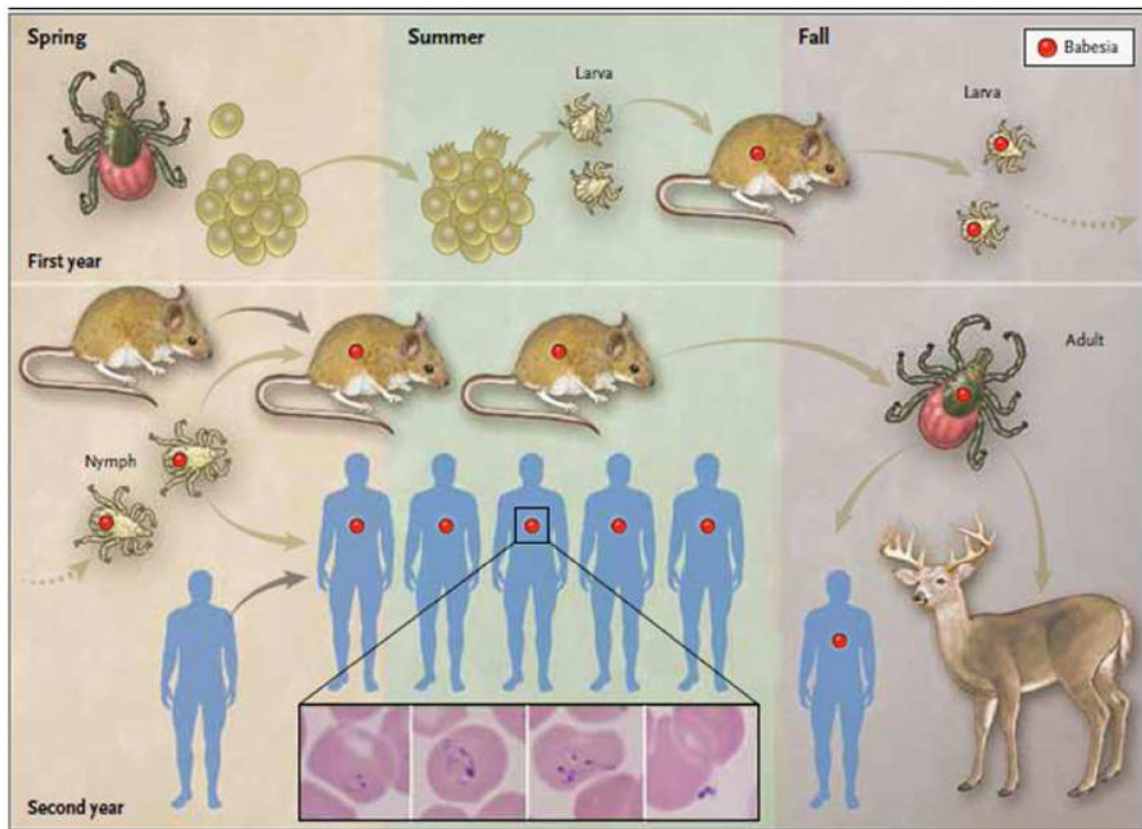
Figure 1. Transmission of *Babesia microti* by the *Ixodes scapularis* tick
Adult female ticks lay eggs in the spring (first year, top left panel).[4] Larvae hatch in the early summer and become infected with *B. microti* (red circle) as they take a blood meal from infected white-footed mice (*Peromyscus leucopus*) in late summer. White-footed mice are the primary reservoir host, but other small rodents may carry *B. microti*. Larvae molt to nymphs the following spring (second year, bottom left panel). When infected nymphs feed on mice or humans in late spring or early summer, these hosts may become infected. Humans are incidental hosts. In the fall, nymphs molt to adults that feed on white-tailed deer (*Odocoileus virginianus*) but rarely on humans. White-tailed deer do not become infected with *B. microti* but amplify the tick population by providing a blood meal for adult ticks. The following spring, adult female ticks lay eggs and the cycle is repeated. *B. microti* are obligate parasites of erythrocytes and typically are visualized on a Giemsa stained thin blood smear (see inset).[2-3] The inset panels from left to right show a ring form with a non-staining vacuole surrounded by cytoplasm (in blue) and a small nucleus (in purple), an amoeboid form, a tetrad (also referred to as Maltese Cross), and an extracellular form. From Vannier E, Krause PJ. Human babesiosis. New Engl J Med 2012;366:2397-407 (reference 2).
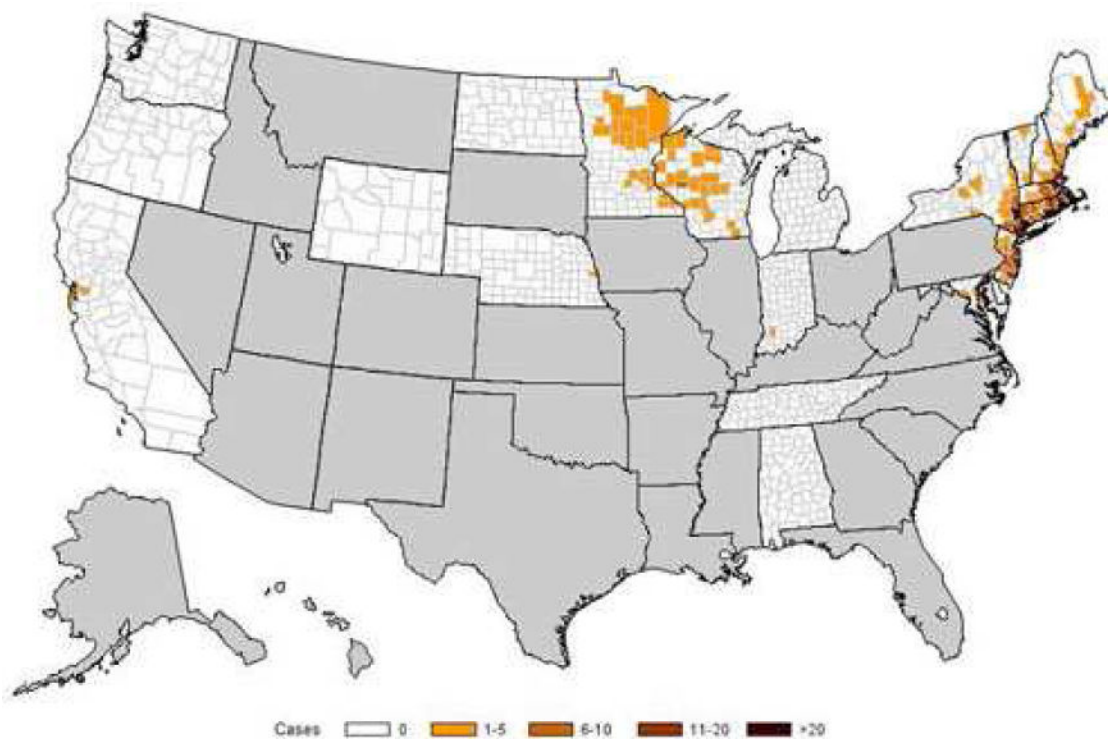
Figure 2. Geographic distribution of human cases of babesiosis in the United States

Babesiosis became a nationally notifiable condition in January 2011. As of 2012, babesiosis is reportable in 22 states and the District of Columbia. The figure shows the incidence of babesiosis (number of cases per 100,000 persons) by county of residence in 2012. Human babesiosis caused by *B. microti* has long been reported from the Northeast, particularly from Massachusetts to New Jersey, and recently became endemic in northern New England (Maine and New Hampshire) and in the northern Mid-Atlantic States (from Pennsylvania to Maryland). *B. microti* also causes disease in the upper Midwest, particularly in Wisconsin and Minnesota. *B. duncani* has been the etiologic agent along the northwest Pacific Coast. Cases of *B. divergens*-like infection have been reported from Washington State, Kentucky and Missouri. Adapted from Centers for Disease Control and Prevention (http://www.cdc.gov/parasites/babesiosis/data-statistics.html).
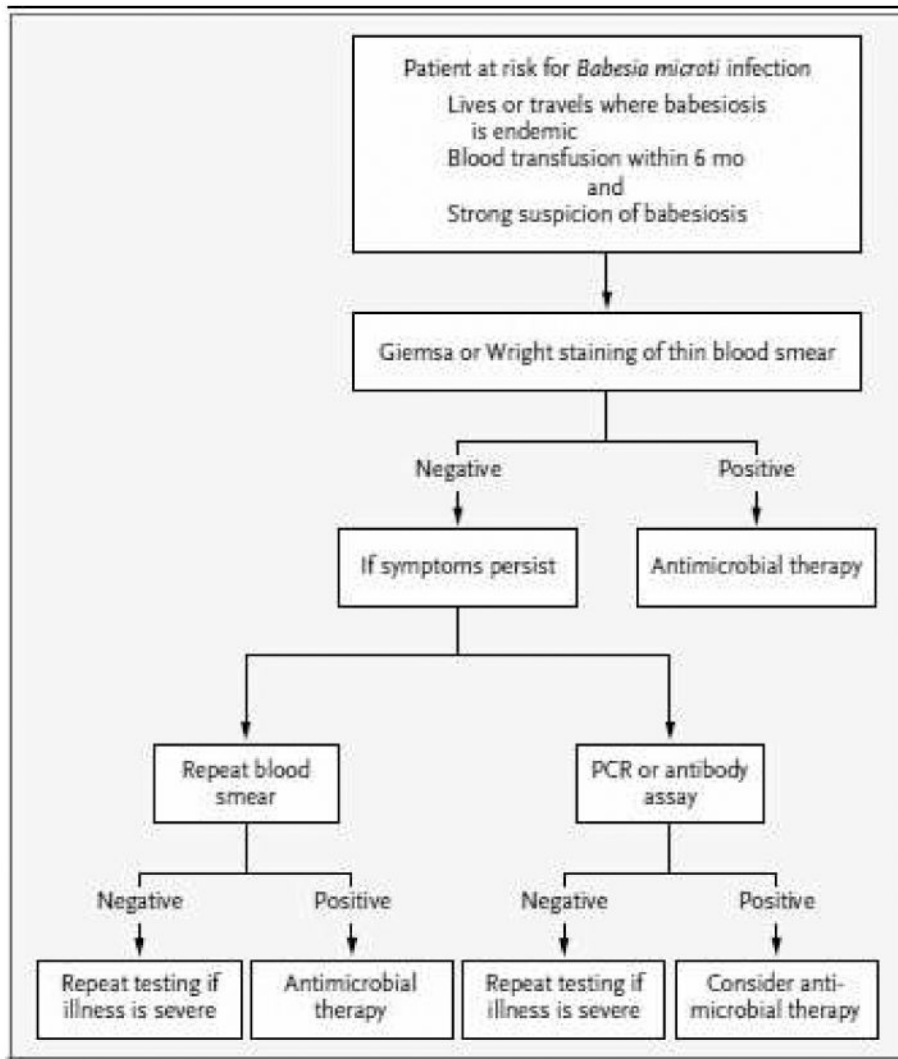
Figure 3. Algorithm for diagnosis of human babesiosis caused by *Babesia microti*

The laboratory diagnosis of babesiosis should only be initiated for patients who are at risk of infection and for whom there is strong suspicion of infection.[2, 10] Laboratory testing is required for definitive diagnosis of babesiosis. From Vannier E, Krause PJ. Human babesiosis. New Engl J Med 2012;366:2397-407 (reference 2).

Table 1

Symptoms of babesiosis

Symptoms	Outpatients (%) (n=41)	Inpatients (%) (n=249)	All patients (%) (n=290)
Fever	88	89	89
Fatigue	85	82	82
Chills	63	68	67
Sweats	73	58	60
Anorexia	56	53	53
Headache	68	44	47
Myalgia	66	39	43
Nausea	32	44	42
Cough	34	27	28
Arthralgia	46	22	25

Outpatient cases are from Ruebush et al. [19], Krause et al. [20], and Krause et al. [21]. Inpatient cases are from White et al. [16], Krause et al. [18], Hatcher et al. [22], and Joseph et al. [14].

Table 2

Treatment of human babesiosis

Antimicrobials	Dose	Frequency
Atovaquone plus azithromycin		
Atovaquone	Adult: 750 mg	Every 12 hours
	Child: 20 mg/kg (maximum 750 mg/dose)	Every 12 hours
Azithromycin	Adult: 500 to 1000 mg	On day 1
	250 to 1000 mg	On subsequent days
	Child: 10 mg/kg (maximum 500 mg/dose)	On day 1
	5 mg/kg (maximum 250 mg/dose)	On subsequent days
Clindamycin plus quinine		
Clindamycin	Adult: 600 mg	Every 8 hours
	Child: 7-10 mg/kg hours (maximum 600 mg/dose)	Every 6-8
	Intravenous administration	
	Adult: 300-600 mg	Every 6 hours
	Child: 7-10 mg/kg hours (maximum 600 mg/dose)	Every 6-8
Quinine	Adult: 650 mg	Every 6-8
	hours Child: 8 mg/kg (maximum 650 mg/dose)	Every 8 hours

All antibiotics are administered by mouth unless otherwise specified. All doses administered for 7 to 10 days except for persistent relapsing infection (see text).