

## REVIEW ARTICLE

## CURRENT CONCEPTS

## Human Babesiosis

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**H**UMAN BABESIOSIS IS AN INFECTIOUS DISEASE CAUSED BY INTRAERYTHROCYTIC protozoa of the genus *babesia*. The disease is named after Victor Babes, the Hungarian pathologist and microbiologist who identified intraerythrocytic microorganisms as the cause of febrile hemoglobinuria in cattle in 1888.<sup>1</sup> Five years later, Theobald Smith and Frederick L. Kilborne identified a tick as the vector for transmission of *Babesia bigemina* in Texas cattle.<sup>2</sup> This seminal observation established for the first time that an arthropod could transmit an infectious agent to a vertebrate host.

The first documented human case of babesiosis was not recognized until about a half century later, when a splenectomized Croatian herdsman rapidly succumbed to an infection subsequently attributed to *B. divergens*.<sup>3</sup> The first case in an immunocompetent person was identified on Nantucket Island, off the coast of Massachusetts, in 1969.<sup>4</sup> The causative agent was *B. microti*, and the vector was the *Ixodes dammini* tick (now referred to as *I. scapularis*).<sup>5</sup> Additional cases occurred on the island, and the disease became known as “Nantucket fever.” During the past decade, the incidence and geographic distribution of babesiosis have increased in the northeastern and upper midwestern regions of the United States. *B. microti* infection is almost as common as Lyme disease in some areas of southern New England, an observation that is consistent with the high prevalence of *B. microti*-infected ticks in the region.<sup>6-8</sup> Babesiosis is now classified as a nationally notifiable disease and is recognized as an emerging health risk in several parts of the world.<sup>9,10</sup>

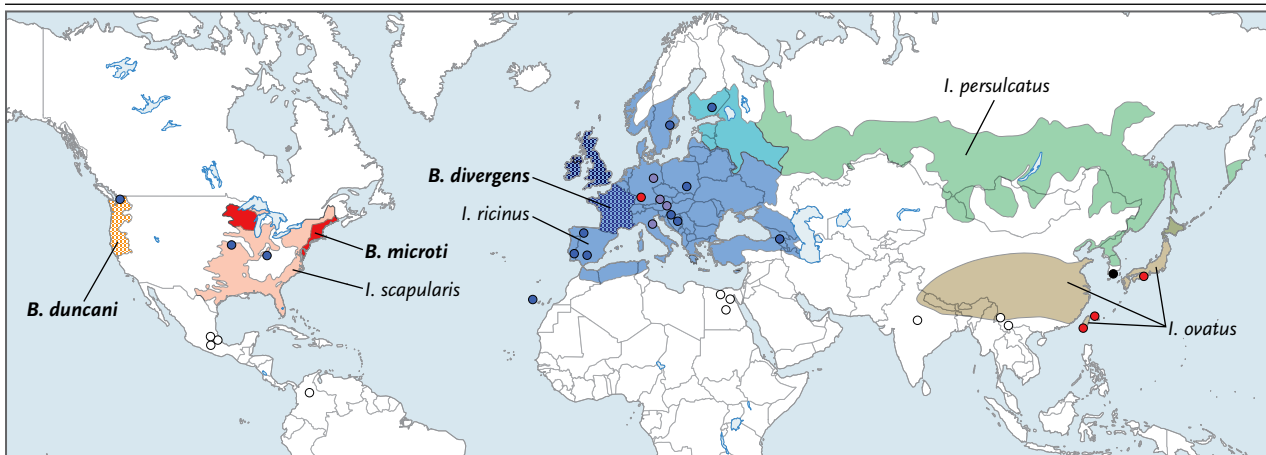
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## EPIDEMIOLOGY AND TRANSMISSION

More than 100 *babesia* species infect a wide array of wild and domestic animals, but only a few have been documented to infect humans.<sup>5,10-12</sup> The overwhelming majority of cases in the United States are caused by *B. microti*. Such cases occur in the Northeast and upper Midwest, primarily from May through October (Fig. 1).<sup>10,12</sup> The emergence of babesiosis in these regions has primarily been attributed to the expansion of the white-tailed deer population, encroachment of local communities on wildlife habitats, and greater awareness of the disease on the part of the public and physicians, although cases remain underreported.<sup>6,33-35</sup> A small number of cases caused by *B. duncani* and *B. duncani*-type organisms have been identified on the Pacific Coast from northern California to Washington State.<sup>14-16</sup> Sporadic cases of infection with *B. divergens*-like organisms have been documented in Kentucky, Missouri, and Washington State.<sup>17-19</sup> In Europe, most reported cases have been attributed to *B. divergens*, and a few have been caused by *B. venatorum* (formerly called EU1) and *B. microti*.<sup>20,22-26</sup> In Asia, *B. microti*-like organisms have caused illness in Japan and Taiwan, whereas a new *babesia* agent (KO1 strain) has been identified in South Korea.<sup>28-31</sup> Sporadic cases of babesiosis have been reported in Africa, Australia, and South America.<sup>15,20,21,27,32</sup>



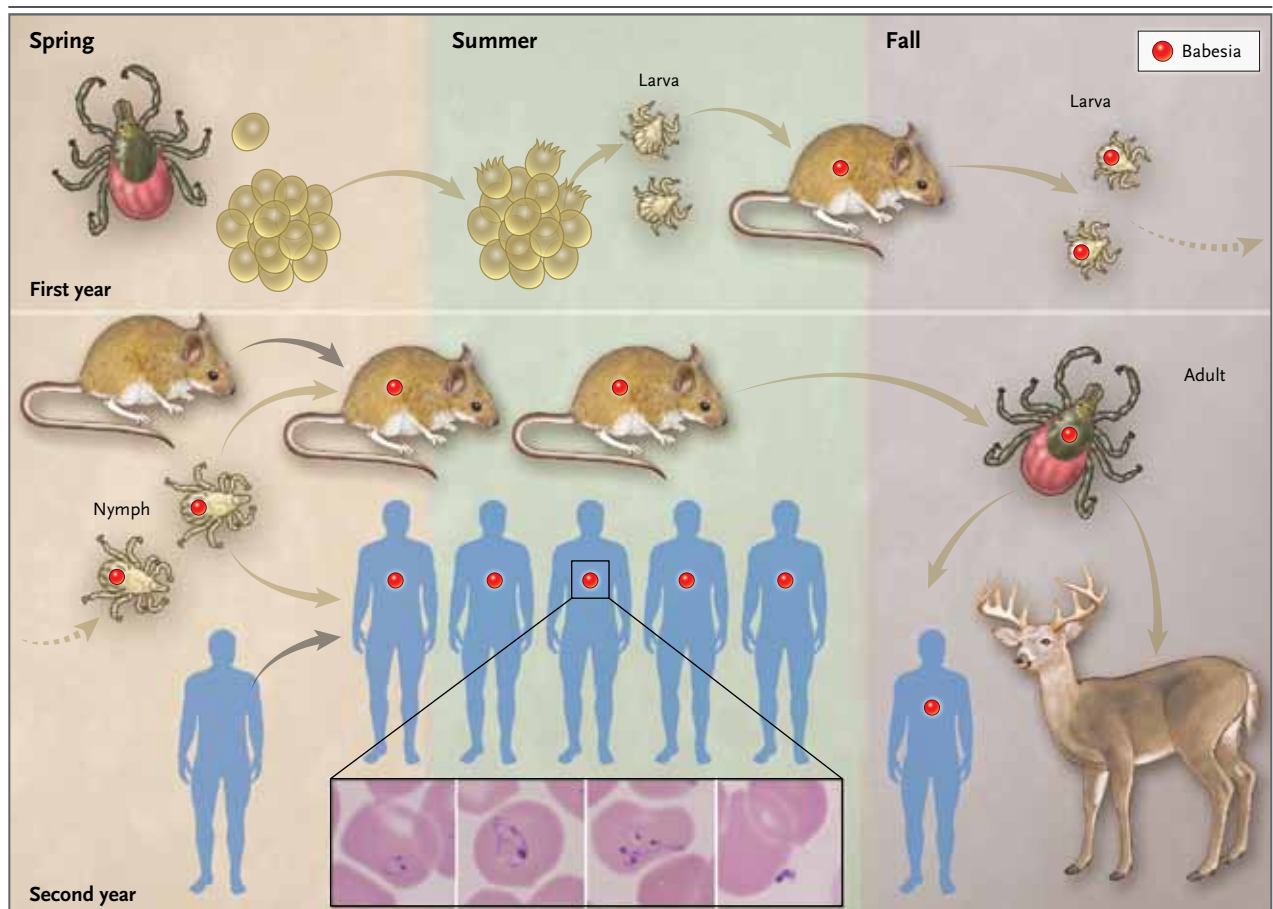
**Figure 1. Geographic Areas Where Human Babesiosis and Ixodes Tick Vectors Are Endemic.**

Light colors denote areas where the ixodes tick vectors that transmit babesia are endemic but where babesiosis has yet to be documented in humans.<sup>13</sup> Dark colors designate areas where human babesiosis is either endemic (solid pattern) or sporadic, as defined by more than three tickborne cases reported in a country or state (stippled pattern). Isolated cases of locally acquired babesiosis are depicted by circles. In the United States, babesiosis caused by *Babesia microti* is endemic in the Northeast and the upper Midwest (dark-red areas), where it is transmitted by *Ixodes scapularis*.<sup>5,6,12</sup> Sporadic cases of babesiosis caused by *B. duncani* or *B. duncani*-type organisms are reported along the northern Pacific Coast (orange stippled area).<sup>14-16</sup> The tick vector is unknown, but *I. pacificus* is the primary candidate.<sup>15</sup> *B. divergens*-like infections have been reported in Missouri, Kentucky, and Washington State (blue circles).<sup>17-19</sup> In South America, symptomatic infections have been acquired in Brazil (not shown) and Colombia (open circle), but the etiologic agents were not molecularly characterized.<sup>20,21</sup> Three asymptomatic cases have been identified in Mexico (open circles).<sup>15</sup> In Europe, *B. divergens* is the primary agent of human babesiosis.<sup>20,22,23</sup> Cases are sporadic in France, Britain, and Ireland (dark-blue stippled areas), but isolated cases have been reported across the continent (blue circles). *B. venatorum* infections have been reported in Austria, Germany, and Italy (purple circles).<sup>24,25</sup> *B. divergens* and *B. venatorum* are phylogenetically related, and both are transmitted by *I. ricinus*. A single case of *B. microti* infection has been reported in Germany (red circle).<sup>26</sup> In Africa, cases caused by uncharacterized babesia species have been documented, including three in Egypt (open circles), one in Mozambique (not shown), and two in South Africa (not shown).<sup>15,27</sup> A case of *B. divergens*-like infection was reported on the Canary Islands, off the coast of western Africa.<sup>23</sup> In Asia, *B. microti*-like organisms caused two cases in Taiwan and one case in Japan (red circles).<sup>28-30</sup> In the latter case, *I. ovatus* ticks infected with *B. microti*-like organisms were found in the area, implicating this tick species as a vector of human babesiosis in Japan. *I. persulcatus* ticks also have been found to transmit *B. microti*-like organisms to mammals but have not yet been established as a vector in human babesiosis. A case in South Korea was caused by the KO1 strain that is related to a species found in sheep (black circle).<sup>31</sup> Cases that were caused by uncharacterized babesia species have been documented in China and India (open circles). In Australia, a definitive case of *B. microti* infection has recently been identified (not shown).<sup>32</sup> Given the widespread distribution of the tick vectors that transmit babesia species in temperate latitudes, the prevalence of human babesiosis may be underestimated, although the endemic range of babesiosis may never reach the enzootic range of the tick species known to transmit babesia to humans.

*B. microti* is primarily transmitted to people by *I. scapularis*.<sup>34</sup> Progression of *I. scapularis* through each of the three stages of its life cycle (larva, nymph, and adult) requires a blood meal from a vertebrate host (Fig. 2). The primary reservoir host for *B. microti* is the white-footed mouse (*Peromyscus leucopus*).<sup>34</sup> Although adult ticks may transmit *B. microti*, most cases result from exposure to nymphal ticks during the period from late spring through summer.<sup>7,34</sup> The tick vectors for transmission of *B. duncani*, *B. duncani*-type, and *B. divergens*-like parasites in the United States have yet to be conclusively identified.<sup>20</sup> In Europe, the sheep tick *I. ricinus* is the primary vector for transmission of *B. divergens* and *B. venatorum*.<sup>20,23,36</sup>

Transplacental transmission of *B. microti* has been reported in a small number of cases.<sup>37</sup>

A few babesia species are transmitted through transfusion of blood or blood products.<sup>38-43</sup> *B. microti* is the most common transfusion-transmitted pathogen reported to the Food and Drug Administration.<sup>38,41,44</sup> More than 150 cases of transfusion-transmitted babesiosis have been identified since the first case was reported in 1979,<sup>45</sup> and three quarters of these cases have occurred since 2000.<sup>46</sup> Three cases have been caused by *B. duncani*.<sup>46,47</sup> The actual number of cases caused by *B. microti* and *B. duncani* is thought to be much greater because many are undetected or under-reported.<sup>41,43,46</sup> Cases of transfusion-transmitted



**Figure 2. Transmission of *Babesia microti* by the *Ixodes scapularis* Tick.**

Adult female ticks lay eggs in the spring.<sup>34</sup> Larvae hatch in the early summer and become infected with *B. microti* 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 into nymphs the following spring. When infected nymphs feed on mice or humans in late spring or early summer, these hosts may become infected. Humans are accidental hosts; most cases of babesia occur from late spring through summer. In the fall, nymphs molt into 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 that are free of *B. microti* (no transovarial transmission) and the cycle is repeated. *B. microti* are obligate parasites of erythrocytes and typically are visualized on a Giemsa-stained thin blood smear (inset).<sup>12,20,23</sup> The inset panels from left to right show a ring form with a nonstaining vacuole surrounded by cytoplasm (blue) and two small nuclei (purple), an amoeboid form, a tetrad (also referred to as a Maltese cross), and an extracellular form.

babesiosis are often severe, since recipients of blood products frequently are immunocompromised or have coexisting medical conditions, and approximately a fifth of cases have been fatal.<sup>46,48,49</sup> Infections are reported throughout the year, but most occur from early summer through late fall.<sup>46,49</sup> About 10% of cases occur in nonendemic areas because persons may become infected at endemic sites and subsequently donate blood in nonendemic areas or because units of contaminated blood are exported to nonendemic areas.<sup>41-43,46</sup>

#### PHYLOGENETIC CLASSIFICATION

*Babesia* species belong to the phylum Apicomplexa, which includes the protozoan parasites causing malaria, toxoplasmosis, and cryptosporidiosis.<sup>11</sup> *Babesia* species that infect humans can be classified into four clades.<sup>16,23,50</sup> The first clade consists of *B. microti*, small parasites (<3  $\mu$ m) that form a species complex in which nearly all human isolates belong to one subclade.<sup>51,52</sup> The second clade includes *B. duncani* and *B. duncani*-type organisms, small babesia that are phylogenetically distinct

from *B. microti* and are related to babesia of dogs and wildlife in the western United States.<sup>15,16</sup> The third clade includes *B. divergens*, a parasite of cattle, and *B. venatorum*, which infects roe deer.<sup>23,24,36</sup> These species are small but phylogenetically related to the large babesia ( $\geq 3 \mu\text{m}$ ). The fourth clade consists of large babesia that infect ungulates and includes the KO1 strain.<sup>23,31</sup>

#### LIFE CYCLE OF PATHOGEN

*B. microti* undergo developmental changes within the tick vector and the reservoir host.<sup>20,23,53</sup> When larval ticks feed on infected mice in late summer (Fig. 2), gametocytes accumulate in the tick gut and differentiate into gametes. Gametes fuse to form zygotes that migrate across the gut epithelium into the hemolymph, where they mature into ookinetes. The ookinetes move to the salivary glands and become dormant sporoblasts.<sup>53</sup> As nymphal ticks feed in the early summer of the following year, several thousand sporozoites are delivered into the vertebrate host. Sporozoites attach to erythrocytes by docking onto glycosaminoglycans and sialoglycoproteins.<sup>54,55</sup> Once inside the erythrocytes, sporozoites mature into trophozoites, which eventually bud to form four merozoites. Egress of merozoites is accompanied by rupture of the host erythrocyte and invasion of other erythrocytes.

#### CLINICAL MANIFESTATIONS

The clinical manifestations of babesiosis range from subclinical infection to fulminating disease resulting in death.<sup>12</sup> Most symptomatic patients become ill 1 to 4 weeks after the bite of a *B. microti*-infected tick and 1 to 9 weeks (but up to 6 months in one reported case) after transfusion of contaminated blood products.<sup>12,46</sup> After a gradual onset of malaise and fatigue, fever usually develops, with a peak temperature that can be as high as 40.9°C (105.6°F). Chills and sweats are common and may be accompanied by headache, myalgia, anorexia, nonproductive cough, arthralgia, and nausea.<sup>6,56-61</sup> Occasional symptoms include vomiting, sore throat, abdominal pain, conjunctival injection, photophobia, weight loss, emotional lability, depression, and hyperesthesia.<sup>12,56</sup> On physical examination, fever is the most common sign. It may be accompanied by splenomegaly or occasionally by pharyngeal erythema, hepatomeg-

aly, jaundice, or retinopathy with splinter hemorrhages and retinal infarcts.<sup>12,56,57</sup>

Laboratory findings that are consistent with a mild-to-moderate hemolytic anemia include a low hematocrit, low hemoglobin level, low haptoglobin level, elevated reticulocyte count, and elevated lactate dehydrogenase level.<sup>58,60,61</sup> Thrombocytopenia is commonly observed. The illness usually lasts for 1 or 2 weeks, but fatigue may persist for months.<sup>56,57,59,62</sup> Asymptomatic parasitemia may persist for several months after standard therapy is initiated or for more than a year if the patient does not receive treatment.<sup>56,62</sup> Illness may relapse in severely immunocompromised patients despite 7 to 10 days of antimicrobial therapy and may persist for more than a year if not adequately treated.<sup>62-66</sup>

The severity of babesiosis depends primarily on the immune status of the patient and on the babesia species causing the infection. About half of children and a quarter of previously healthy adults who are infected with *B. microti* have no symptoms.<sup>6</sup> Asymptomatic, mild, and moderate infections generally occur in people who are immunocompetent.<sup>6,12,33</sup> In contrast, severe *B. microti* illness requiring hospital admission is common among patients who have undergone splenectomy and those with cancer, human immunodeficiency virus infection, hemoglobinopathy, or chronic heart, lung, or liver disease.<sup>49,60,63-66</sup> Other groups at increased risk for severe disease include neonates, persons over the age of 50 years, patients receiving treatment with immunosuppressive drugs for cancer (e.g., rituximab) or undergoing organ transplantation, and those receiving anti-cytokine therapy (e.g., etanercept and infliximab).<sup>25,37,58,60,65-69</sup> Complications develop in approximately half of patients who are hospitalized with babesiosis. The acute respiratory distress syndrome and disseminated intravascular coagulopathy are the most common complications, but congestive heart failure, coma, liver failure, renal failure, or splenic rupture also may occur.<sup>12,58,60</sup> Fatality rates of 6 to 9% have been reported among hospitalized patients and up to 21% among those with immunosuppression.<sup>58,60,65</sup> Cases caused by *B. duncani* and *B. duncani*-type organisms have ranged from asymptomatic to fatal.<sup>14,15,47</sup> Most reported cases of *B. divergens* infection are severe and occur in people who lack a spleen.<sup>20,22</sup> The fatality rate for *B. divergens* infection has dramatically declined since the introduction of aggres-



sive treatment with a combination of antimicrobial agents and exchange transfusion.<sup>20,22</sup> All five reported cases of *B. divergens*-like infection occurred in asplenic patients and were severe, resulting in the deaths of two patients.<sup>17-19,23</sup>

#### HOST RESISTANCE AND PATHOGENESIS

Our understanding of host resistance against babesia species that infect humans is limited and based on human case studies and studies of babesiosis in natural vertebrate hosts and animal models. Splenectomy is a major risk factor for severe infection, regardless of the babesia species.<sup>58,60,64-66,70</sup> The spleen plays a central role in host defense by clearing infected erythrocytes from the bloodstream and mounting a protective immune response (Fig. 3).<sup>71-74</sup> CD4+ T cells in mice with *B. microti* infection and natural killer cells in those with *B. duncani* infection produce interferon- $\gamma$ , the prototypic type 1 helper T-cell (Th1) cytokine that promotes killing of intracellular pathogens by macrophages and enhances antibody production by B cells.<sup>75-77</sup> B cells are critical for resolution of *B. microti* infection in patients whose cellular immunity is impaired and most likely help to clear *B. microti* in immunocompetent patients.<sup>25,65,69</sup> The age-related decline in cellular immunity helps explain the severity of babesiosis in patients over the age of 50 years. In a mouse model of age-related susceptibility to *B. microti* parasitemia, the protection conferred by adoptive transfer of splenic immune cells is age-dependent and genetically determined.<sup>78</sup>

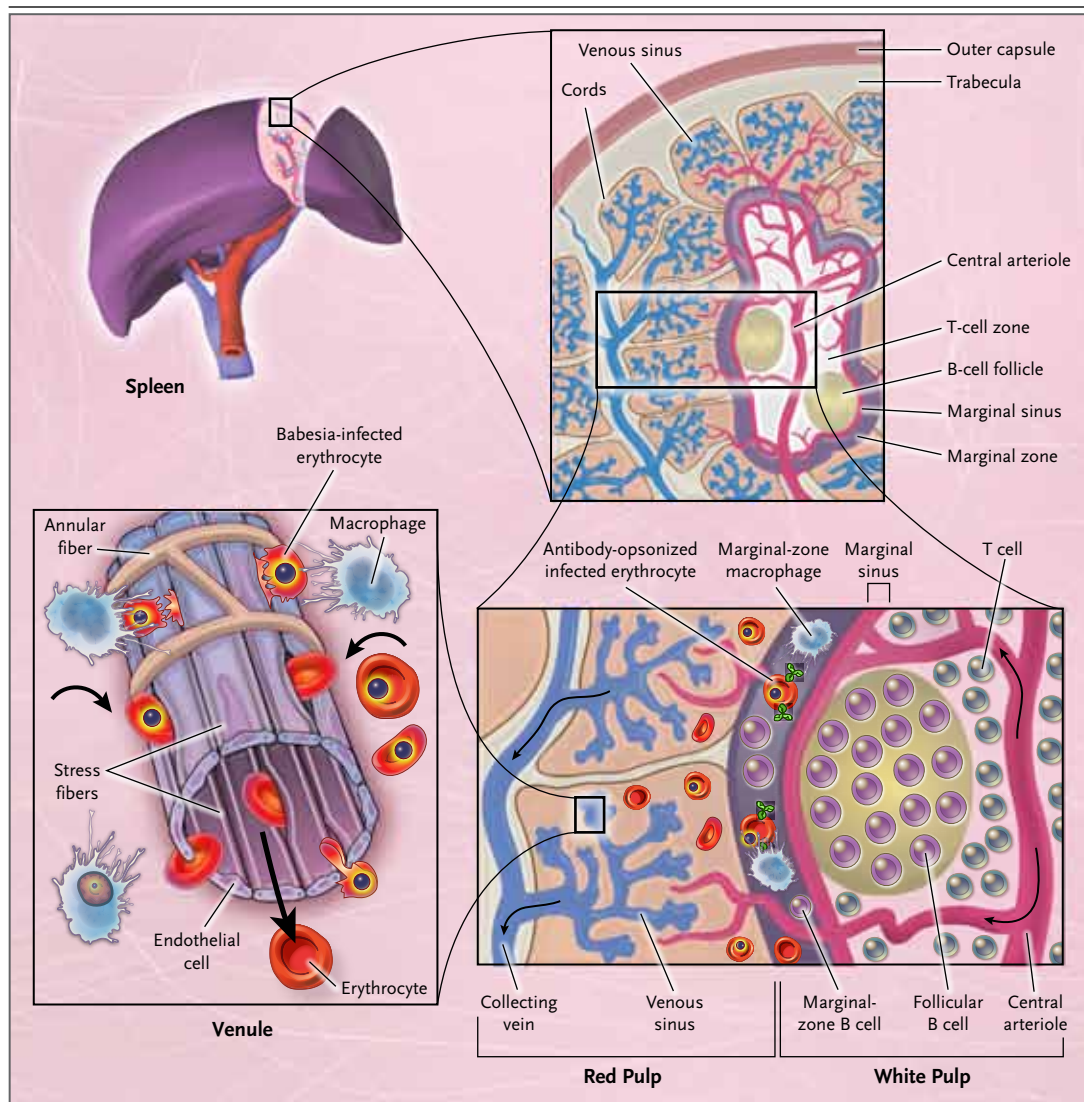
The pathogenesis of babesiosis is closely linked to the host response to infection and parasite-induced modifications in the erythrocyte membrane. In mild cases of babesiosis, inflammatory cytokines (e.g., tumor necrosis factor  $\alpha$  [TNF- $\alpha$ ] and interleukin-6) and adhesion molecules (e.g., E-selectin, intracellular adhesion molecule 1 [ICAM-1], and vascular-cell adhesion molecule 1 [VCAM-1]) are up-regulated.<sup>29</sup> Excessive synthesis of cytokines, however, may result in severe babesiosis and associated complications.<sup>72</sup> Pulmonary inflammation in mice with *B. duncani* infection has been associated with excessive production of TNF- $\alpha$  and interferon- $\gamma$ , and blockade of either cytokine prevents death.<sup>77,79,80</sup> Intravascular sequestration of leukocytes and infected erythrocytes may lead to obstruction of the mi-

crovasculature and tissue hypoxia.<sup>72,81,82</sup> Some babesia species export proteins to the surface of infected erythrocytes, resulting in the adherence of these erythrocytes to the vascular endothelium and in their delayed clearance by the spleen.<sup>82</sup> As with *Plasmodium falciparum*, the protein that is critical for cytoadherence of *B. bovis*-infected erythrocytes is encoded by a variable multicopy gene family that contributes to immune evasion.<sup>72,82</sup> Cytoadherence of babesia-infected erythrocytes has yet to be documented in humans. Anemia that is caused by the rupture of erythrocytes during egress of babesia also contributes to pathogenesis, as do nonhemolytic mechanisms, such as the clearance of uninfected erythrocytes.<sup>83</sup>

#### DIAGNOSIS

Babesiosis should be considered in any patient with an unexplained febrile illness who has resided in or traveled to an area where the infection is endemic within the previous 2 months or who has received a blood transfusion within the previous 6 months (Fig. 4).<sup>12,39,43,46,84</sup> The diagnosis requires a strong clinical suspicion because of the lack of an easily recognized clinical sign, such as the erythema migrans rash of Lyme disease. Since *I. scapularis* ticks can transmit *B. microti*, *Borrelia burgdorferi*, and *Anaplasma phagocytophilum*, babesiosis should be suspected in patients in whom Lyme disease or anaplasmosis has been diagnosed if more severe disease develops or if they have a poor response to standard antimicrobial therapy.<sup>7,8,57,84,91</sup>

A definitive diagnosis is generally made by microscopical identification of babesia on thin blood smears with Giemsa or Wright staining (Fig. 2).<sup>12,15,20,23</sup> *B. microti* trophozoites appear as pleomorphic ring forms (round, oval, pear-shaped, or amoeboid) and are indistinguishable from *B. duncani* trophozoites. Although rare, tetrads of merozoites that are arranged in a cross-like pattern (a so-called Maltese cross) are pathognomonic for babesiosis caused by *B. microti* or *B. duncani*.<sup>12,16</sup> *B. divergens* and *B. venatorum* merozoites typically appear as paired pear-shaped forms but also rarely appear as tetrads in human red cells.<sup>20,24</sup> Although ring forms of babesia may resemble those of *P. falciparum*, malaria can be eliminated from consideration on the basis of a travel history and a careful review of blood smears.<sup>12,15,20</sup> Distinguishing features of babesia



**Figure 3. The Splenic Response to Babesia Infection.**

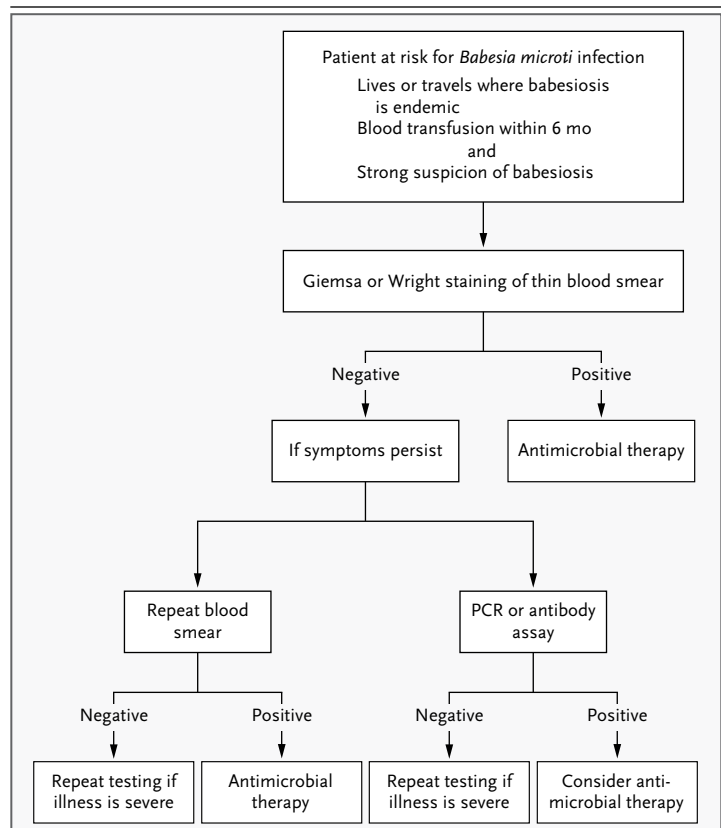
The following composite model is based on studies of babesia infection in natural vertebrate hosts and animal models.<sup>12,71-77</sup> The spleen is a heavily vascularized organ (top left panel) that consists of red-pulp zones and white-pulp zones surrounded by a trabecula and an outer capsule.<sup>71,74</sup> A circulating erythrocyte travels through the spleen approximately once every 20 minutes. Erythrocytes enter the spleen by means of the trabecular artery and flow into central arteries and follicular arterioles to reach the marginal sinus of the white pulp. Once in the adjacent marginal zone, babesia-infected erythrocytes are ingested and destroyed by resident dendritic cells and macrophages.<sup>73</sup> Marginal-zone macrophages do not express major histocompatibility complex (MHC) class II molecules but shed pathogen-degradation products that are picked up by marginal-zone B cells.<sup>71</sup> Activated marginal-zone B cells and dendritic cells move to the T-cell zones, where they present antigen to T cells. Activated T cells migrate to the edge of the follicles and engage B cells, causing them to activate and eventually differentiate into antibody-secreting cells. Opsonization of babesia-infected erythrocytes by antibody promotes their clearance by phagocytes. Activated T cells also produce interferon- $\gamma$ , the prototypic cytokine that helps macrophages kill ingested pathogens.<sup>75,76</sup> Blood may bypass the white pulp and reach the red pulp directly.<sup>71,74</sup> In the splenic cords of the red pulp, blood cells slowly flow between reticular fibers and are sensed by resident macrophages. Babesia-infected erythrocytes squeeze with difficulty through the apertures of the endothelium lining and are ingested by resident macrophages of the cords. Stress fibers that run longitudinally at the base of the endothelial-cell lining and connect to annular fibers can contract and loosen, thereby regulating the flow and size of erythrocytes that reach the venous sinuses. Blood cells that access the venous sinuses flow into venules and eventually reach the collecting vein.

are pleomorphic ring forms, extracellular forms, the absence of identifiable gametocytes, and the absence of brown deposits (hemozoin). The level of parasitemia is generally between 1 and 10% but can be as high as 80%.<sup>12,58,60,70</sup> Because the parasitemia level is often less than 1% early in the course of illness, at least 300 microscopical fields should be reviewed (Fig. 4).

Other laboratory tests are useful in establishing the diagnosis, especially when smears are negative. A polymerase-chain-reaction (PCR) assay is highly sensitive and specific for the detection of babesia DNA in blood, particularly with real-time technology.<sup>85,86</sup> The standard assay for the detection of babesia antibody is the indirect immunofluorescence assay.<sup>87-89</sup> IgM antibody usually is first detected 2 weeks after the onset of illness.<sup>89</sup> IgG titers often exceed 1:1024 during the acute phase of illness and decline to 1:64 or less within 8 to 12 months.<sup>62,87</sup> An immunoblot assay for detection of *B. microti* antibody is also available.<sup>90</sup> Assays for *B. microti* antibody do not detect *B. duncani*, *B. divergens*, or *B. venatorum* antibody.<sup>14,15,20,43</sup> When laboratory tests are inconclusive and infection is strongly suspected, a blood sample from the patient can be injected into a laboratory animal, such as a hamster. *B. microti* organisms usually appear in the blood of the inoculated animal within 2 to 4 weeks.<sup>85</sup>

#### TREATMENT AND OUTCOME

A combination of atovaquone and azithromycin is the treatment of choice for immunocompetent patients with mild-to-moderate babesiosis (Table 1).<sup>59,92</sup> One study showed that this combination was as effective as clindamycin and quinine in clearing parasitemia and resolving symptoms.<sup>59</sup> Only 15% of 41 patients receiving atovaquone and azithromycin had symptoms consistent with an adverse drug reaction, and only 1 patient (2%) had to discontinue the medications because of side effects. In contrast, three fourths of 18 patients receiving clindamycin and quinine had adverse drug reactions, and dose reduction or discontinuation of treatment was required in a third of these patients. Even patients with mild babesiosis should be treated with atovaquone and azithromycin because without treatment, the infection may not be cleared and severe disease may develop or the patients may inadvertently transmit the infection by donating blood. Treatment



**Figure 4. Algorithm for Diagnosis of Babesiosis Caused by *Babesia microti*.**

Diagnostic laboratory testing for babesiosis should be initiated only if there is a strong suspicion of infection and the patient is at risk for infection (because of residence in or travel to an area where babesiosis is endemic or receipt of a blood transfusion within the previous 6 months).<sup>12,39,43,46,84</sup> An example would be a patient living in an area where babesiosis is endemic, who is seen in the summertime for fever lasting more than 2 days with no apparent cause, and who removed an engorged tick within the past month. Babesiosis also should be considered in a patient with Lyme disease or human granulocytic anaplasmosis who reports symptoms that are more severe than usual or who has a poor response to standard antimicrobial therapy.<sup>57,84</sup> Laboratory testing is required for definitive diagnosis of babesiosis. Initial testing should consist of Giemsa or Wright staining of thin blood smears with oil immersion.<sup>12,20,23</sup> Babesia are often too small to be readily visualized on thick smears.<sup>15</sup> Automated hematology analyzers are not reliable in detecting babesia-infected erythrocytes.<sup>15,20</sup> Since the level of parasitemia may be low when the patient is first seen, additional thin blood smears may be required over the course of several days to detect the organism. Smears typically are repeated every 12 to 24 hours. When smears remain negative but the diagnosis is strongly suspected, a babesia-specific polymerase-chain-reaction (PCR) assay should be performed and if positive, antimicrobial therapy should be considered.<sup>85,86</sup> Detection of babesia antibody in serum may be helpful in making the diagnosis, but treatment that is based on positive serologic analysis alone should be avoided. Antibodies are detected by means of indirect immunofluorescence assay or immunoblotting.<sup>87-90</sup> High IgG titers ( $\geq 1:1024$ ) are indicative of active or recent infection. The presence of IgM ( $\geq 1:64$ ) without IgG antibody suggests either very recent infection or a false positive antibody reaction. Injection of the patient's blood into small rodents is useful when symptoms persist and other laboratory tests remain negative.<sup>85</sup>

**Table 1. Antimicrobial Treatment of Human Babesiosis.\***

Treatment		Dose
Atovaquone and azithromycin†		
Atovaquone	Adult, 750 mg; pediatric, 20 mg/kg (maximum, 750 mg/dose) every 12 hr	
Azithromycin	Adult, 500 mg on day 1 and 250 mg on subsequent days; pediatric, 10 mg/kg (maximum, 500 mg/dose) on day 1 and 5 mg/kg (maximum, 250 mg/dose) on subsequent days	
Clindamycin and quinine		
Clindamycin		
Oral	Adult, 600 mg every 8 hr; pediatric, 7–10 mg/kg (maximum, 600 mg/dose) every 6–8 hr	
Intravenous	Adult, 300–600 mg every 6 hr; pediatric, 7–10 mg/kg (maximum, 600 mg/dose) every 6–8 hr	
Quinine	Adult, 650 mg every 6–8 hr; pediatric, 8 mg/kg (maximum, 650 mg/dose) every 8 hr	

\* All doses of antimicrobial therapy are administered for 7 to 10 days, except in patients with persistent relapsing infection, who receive such therapy for at least 6 weeks, including 2 weeks after babesia are no longer detected on a blood smear. Complete or partial exchange transfusion is recommended for babesiosis caused by *Babesia divergens* but should also be considered for any severe case of babesiosis caused by other babesia species, including *B. microti* and *B. duncani*. All antimicrobial agents are administered by mouth unless otherwise specified.

† For immunocompromised patients with babesiosis, successful outcomes have been reported with the use of atovaquone combined with higher doses of azithromycin (600–1000 mg per day).

of asymptomatic carriers should be considered if parasites are detected for longer than 3 months.<sup>92</sup>

The combination of clindamycin and quinine was the first successful antimicrobial regimen for the treatment of *B. microti* infection,<sup>93</sup> and intravenous clindamycin and oral quinine are still recommended for patients with severe babesial illness (Table 1).<sup>92</sup> When necessary, intravenous quinidine can be used instead of oral quinine but requires cardiac monitoring for possible prolongation of the QT interval. Partial or complete exchange transfusion of whole blood or packed red cells should be considered in patients with severe disease, particularly those infected with *B. divergens*.<sup>12,20,23,45,94</sup> Indications for such therapy include a high level of parasitemia ( $\geq 10\%$ ), clinically significant anemia, or renal, hepatic, or pulmonary compromise.<sup>12,60,64,92</sup>

Severely immunocompromised patients may have persistent or relapsing babesiosis despite treatment with the standard course of 7 to 10 days of antimicrobial agents.<sup>65</sup> In such patients, a cure generally requires at least 6 weeks of antimicrobial therapy, including 2 weeks after babesia are no longer detected on blood smears.<sup>65</sup> High doses of azithromycin in combination with atovaquone have been used successfully in immunocompromised patients (Table 1).<sup>95</sup> Resistance to atovaquone and azithromycin occasion-

ally develops during prolonged therapy (>4 weeks) that follows an initial, subcurative course of this combination.<sup>66</sup>

Patients with babesiosis should be closely monitored during therapy. In most cases, symptoms abate within a day or two after antimicrobial therapy is initiated, and infection resolves within 3 months.<sup>59,62,92</sup> In severely ill patients, parasitemia should be monitored daily until it has decreased to a level of less than 5% and the patient's condition has improved. If symptoms recur, treatment should immediately resume, with close clinical follow-up.

## PREVENTION

Preventive measures consist of personal, residential, and community approaches.<sup>35,96–99</sup> Personal protective measures include avoiding sites where ticks, mice, and deer thrive. It is especially important for persons at increased risk, such as asplenic or other immunocompromised persons who live in or travel to areas where babesiosis is endemic, to avoid deciduous forests and the edge between woodlands and open areas, where ticks may abound.<sup>35,96,97</sup> Persons who cannot avoid such areas should wear protective clothing, apply tick repellents containing permethrin or *N,N*-diethyl-meta-toluamide (DEET) to clothing and repellents



containing DEET to skin, and examine themselves daily for ticks.<sup>98</sup> Landscape-management strategies, such as keeping grass mowed, removing leaf litter, using plantings that do not attract deer, and spraying areas of high tick density with acaricidal formulations, may help reduce the risk of tickborne infections.<sup>97,99</sup> The elimination of deer populations sharply reduces the risk of infection but is difficult to implement.<sup>35</sup> Public education about the risks and characteristic symptoms of tickborne diseases is an important part of these preventive measures.

The current approach of questioning prospective blood donors about a history of babesiosis and indefinitely deferring those who have had the disease has not been effective in preventing transfusion-transmitted babesiosis.<sup>39,41,43</sup> Laboratory-based screening programs to identify prospective blood donors who are infected with babesia are being developed for use in areas where babesiosis is endemic. An interim analysis

of the first such program showed that the combined use of an indirect immunofluorescence assay to detect *B. microti* antibody and a real-time PCR assay to detect *B. microti* DNA reduced the incidence of transfusion-transmitted babesiosis in neonates and children with sickle cell disease or thalassemia.<sup>100</sup> On the basis of the recent emergence of tickborne and transfusion-transmitted babesiosis, the development of a vaccine against human babesiosis should be considered.

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