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Invited Review

Human babesiosis

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ABSTRACT

Babesiosis is a worldwide emerging tick-borne disease that is increasing in frequency and geographic range. It imposes a significant health burden, especially on those who are immunocompromised and those who acquire the infection through blood transfusion. Death from babesiosis occurs in up to 20 percent of these groups. Diagnosis is confirmed with identification of typical intraerythrocytic parasites on a thin blood smear or *Babesia* DNA using PCR. Treatment consists of atovaquone and azithromycin or clindamycin and quinine, and exchange transfusion in severe cases. Personal and communal protective measures can limit the burden of infection but it is important to recognize that none of these measures are likely to prevent the continued expansion of *Babesia* into non-endemic areas.

1. Introduction

Babesiosis is a disease caused by intraerythrocytic protozoa with many clinical features that are similar to those of malaria. Unlike the malaria parasite, *Babesia* spp. circulate in a natural tick-reservoir host cycle and are usually transmitted to humans through the bite of an infected tick, occasionally through blood transfusion, and rarely through perinatal transmission or organ transplantation (Spielman et al., 1985; Herwaldt et al., 2011; Cornett et al., 2012; Vannier and Krause, 2012). Victor Babes first described the parasite in 1888 in Romanian cattle while Smith and Kilbourne identified ticks as the mode of transmission in 1893 in Texas cattle (Babes, 1888; Smith and Kilbourne, 1893). The first human case was described by Skrabalo and Deanovic in Yugoslavia in 1957 (Skrabalo and Deanovic, 1957). During the past 50 years, an increasing number of species of *Babesia* have been shown to infect humans and an increasing number of cases have been reported worldwide, particularly in the United States. Infection is usually mild to moderate. Severe disease that can cause complications and death may occur, primarily in those with comorbidities or who are immunocompromised.

2. Epidemiology

2.1. Babesia spp.

Most *Babesia* spp. are small (1–5 μm in length) and appear pear-shaped, round, or oval (Healy and Ruebush, 1980). *Babesia microti* has the smallest nuclear genome of all parasites in the phylum Apicomplexa studied so far, including *Plasmodium*, *Toxoplasma*, and *Cryptosporidia*, and has the minimal metabolic requirement for intraerythrocytic protozoan parasitism (Cornillot et al., 2012; Carpi et al., 2016; Lemieux et al., 2016; Silva et al., 2016). More than 100 *Babesia* spp. have been identified in wild and domestic animals. *Babesia* that infect livestock have had a significant worldwide economic impact and include *Babesia bigemina, Babesia bovis, Babesia divergens* and *Babesia major*. Other animals infected by *Babesia* spp. include horses (*Babesia caballi*), dogs (*Babesia canis*), cats (*Babesia felis*), deer (*Babesia odocolei*), and rodents (*B. microti*) (Levine, 1971). Several *Babesia* spp. have been found to cause disease in humans. These are *B. microti, Babesia crassa*-like pathogen, *B. divergens, Babesia duncani,* and *Babesia venatorum*, as well as several other *Babesia* that are closely genetically related (*B. divergens*–like, *B. duncani*-type, *B. microti*-like) or described in a single case (K01, XXB/Hang/Zhou) (Table 1, Fig. 1).

2.2. Human babesiosis in the United States

The great majority of cases worldwide have been those caused by *B. microti* from the northeastern and northern midwestern regions of the United States where the disease is endemic. An increase from approximately 1,000 cases per year to 2,000 cases per year has been recorded since national reporting began in 2011 but this is thought to be an underestimate of the true number of cases due to asymptomatic infection, failure to report cases, and misdiagnosis. In a prospective 10 year study at a highly endemic site, approximately a quarter of adults and half of children experienced asymptomatic infection, and the incidence of babesiosis approached that of Lyme disease (Krause et al., 2003). Most cases

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Table 1
Babesia spp. causing infection in humans and their vectors.

Babesia spp.	Probable or confirmed vector
Asia	
Babesia crassa-like	*Ixodes persulcatus, Haemaphysalis concinna*
Babesia microti	*Ixodes persulcatus, Ixodes ovatus*
Babesia venatorum	*Ixodes persulcatus*
KO-1	*Ixodes* spp.
XXB/HangZhou	*Ixodes* spp.
Europe	
Babesia divergens	*Ixodes ricinus*
Babesia microti	*Ixodes ricinus*
Babesia venatorum	*Ixodes ricinus*
United States	
Babesia microti	*Ixodes scapularis*
Babesia duncani	*Dermacentor albipictus*
Babesia divergens-like	*Ixodes* spp.

of babesiosis occur from late spring through early autumn in the United States in areas where the vector tick, rodents and deer are in close proximity to humans.

Over the past two decades, the number of *B. microti* infections has increased and the geographic range has expanded in the northeastern and midwestern United States (Krause et al., 1991; White et al., 1998; Rodgers and Mather, 2007; Joseph et al., 2011; Smith et al., 2014; Stein et al., 2015; Walter et al., 2016; Mareedu et al., 2017; Goethert et al., 2018). An increase in the number of white tailed deer is thought to help account for the increasing incidence of all *Ixodes scapularis*-transmitted pathogens, as deer act to amplify the *Ixodes* tick population (Spielman et al., 1985). Increased housing construction in wooded areas, greater recognition of these diseases by physicians and the general public, and more accessible diagnostic testing also are thought to contribute to the emergence of *Ixodes* tick-borne diseases. The range expansion of *B. microti* has proceeded from southern New England to the west, north and south but more slowly than that of *Borrelia burgdorferi* (Dunn-Krause et al., 2014; Diuk-Wasser et al., 2016; Walter et al., 2016) (Fig. 2). Several hypotheses have been proposed for this differential expansion. Birds serve as reservoirs for *B. burgdorferi* but not *B. microti*. Thus, larval ticks may become infected with *B. burgdorferi* by feeding on birds and these infected larvae can be deposited hundreds of miles away where they molt to infected nymphs and establish a new site of infection. In contrast, *B. microti* can only spread when infected mice move to a new area, hence the saying that *B. burgdorferi* spreads on the wings of birds and *B. microti* on the backs of mice (Spielman et al., 1985; Walter et al., 2016; Goethert et al., 2018). In addition, *B. burgdorferi* is transmitted more readily than *B. microti* from rodent reservoir hosts to the *I. scapularis* tick vector. Experiments in laboratory-bred *Peromyscus leucopus* mice, the natural reservoir host, have indicated that coinfection with the Lyme disease spirochete can enhance *B. microti* parasitemia in the mouse and increase the transmission of *B. microti* (Dunn-Krause et al., 2014; Diuk-Wasser et al., 2016). Experimental modeling based on this data suggests that *B. microti* may not be able to move into a new region until *B.*

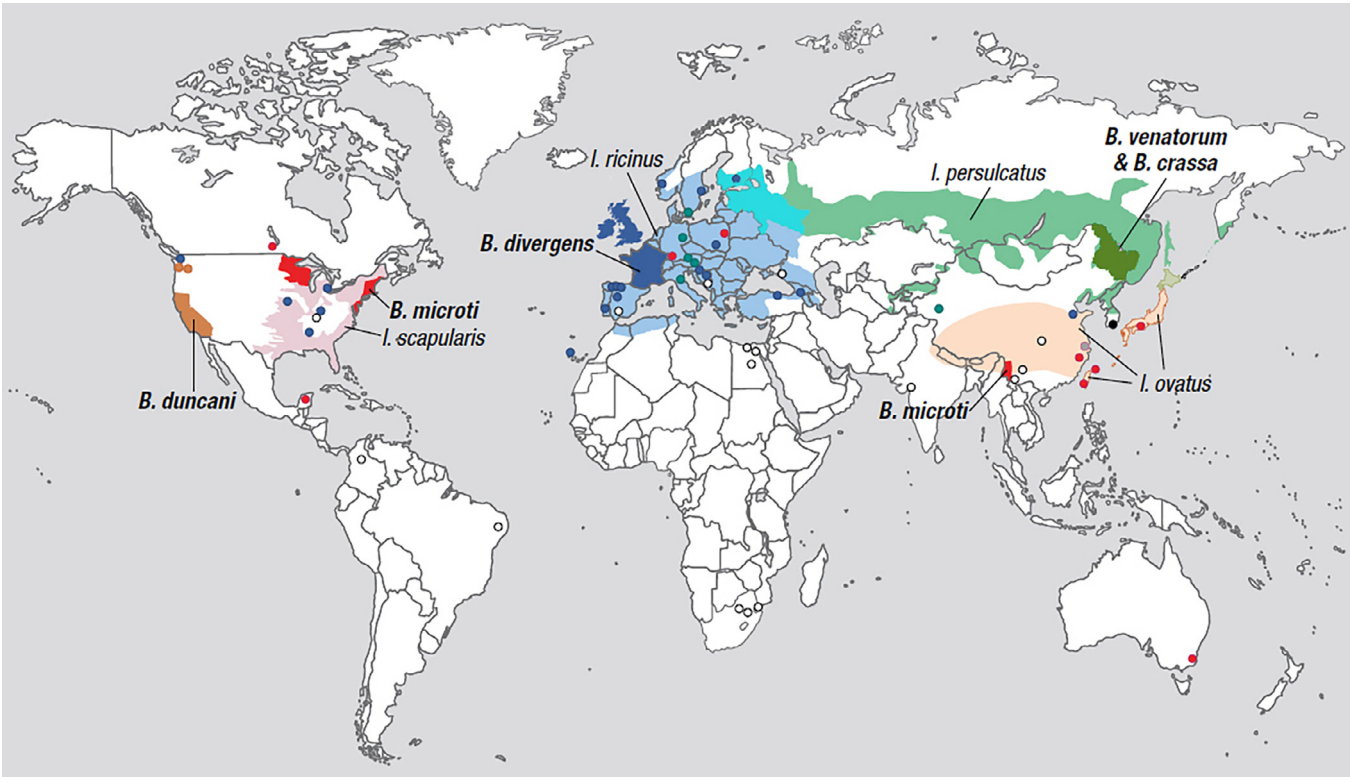

Fig. 1. Worldwide distribution of human babesiosis and *Ixodes* tick vectors. The global distribution of human babesiosis and its tick vectors are shown. Dark colors indicate areas where human babesiosis is endemic or sporadic (defined by ≥5 cases). Light colors indicate areas where tick vectors are present but human babesiosis is rare (<5 cases), undocumented, or absent. Enzootic areas for *I. persulcatus* and *I. ricinus* overlap in southern Finland, Estonia, Latvia, and northwestern Russia. Enzootic areas for *I. ovatus* and *I. persulcatus* overlap on the island of Hokkaido in northern Japan. Circles depict single cases, except in three locations (Mexico, Montenegro, and eastern Poland) where all patients lived in the same area. Colors distinguish the etiologic agents: red for *Babesia microti*, orange for *Babesia duncani*, blue for *Babesia divergens*, green for *Babesia venatorum*, black for KO-1, and gray for *Babesia* spp. XXB/HangZhou. White circles depict cases caused by uncharacterized *Babesia* spp. Asymptomatic infections are omitted. Note that a few cases of *B. crassa*-like infection have been reported in northeastern China, the same region where *B. venatorum* is endemic (adapted from New England Journal of Medicine, Vannier E., Krause P.J. Human babesiosis. 2012; 366: 2398. Copyright © (2019) Massachusetts Medical Society. Reprinted with permission; and from Vannier E., Krause P.J. 2019. Babesiosis. Ryan ET, Hill DR, Solomon T, Aronson NE, Endy TP (Eds); Hunter's Tropical Medicine and Emerging Infectious Disease 10th ed; © Elsevier; 2020; in press).

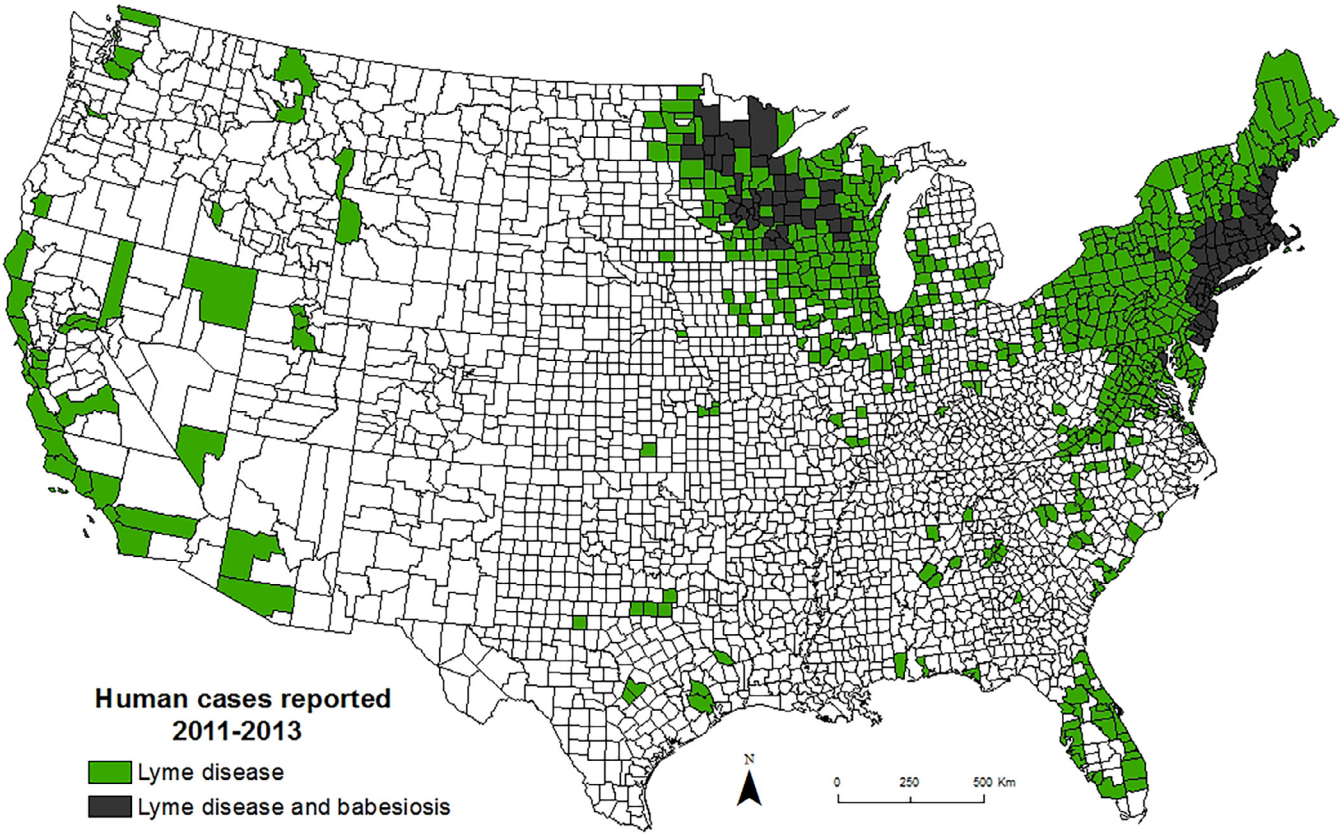

Fig. 2. Human babesiosis in counties endemic for Lyme disease in the United States. Lyme disease and human babesiosis are disbursing geographically but Lyme disease has spread more rapidly than babesiosis. Lyme disease has been a nationally notifiable condition since 1991 and human babesiosis since 2011. The names of counties that reported cases of Lyme disease and/or babesiosis from 2011 to 2013 were obtained from the Centers for Disease Control and Prevention (adapted from Diuk-Wasser M., Vannier E., Krause P.J., 2016. Coinfection by *Ixodes* tick-borne pathogens: Ecological, epidemiological, and clinical consequences. Trends in Parasitology 32, 30–42). Counties with three or more cases of Lyme disease but fewer than three cases of babesiosis are depicted in green. Counties with three or more cases of Lyme disease and three or more cases of babesiosis are depicted in gray. No county reported three or more cases of babesiosis but fewer than three cases of Lyme disease (adapted from Diuk-Wasser, M., Vannier, E., Krause, P.J., 2016. Coinfection by *Ixodes* tick-borne pathogens: Ecological, epidemiological, and clinical consequences. Trends Parasitol. 32, 30–42).

burgdorferi has first become established there (Dunn-Krause et al., 2014; Diuk-Wasser et al., 2016).

Human babesiosis caused by *B. duncani* and *B. duncani*-type organisms have been reported over a broad range on the west coast from California to Washington State, although fewer than 20 cases have been described (Kjemtrup and Conrad, 2000; Conrad et al., 2006). Cases of babesiosis due to *B. divergens*-like organisms have been reported in Arkansas, Kentucky, Missouri and Washington State (Herwaldt et al., 2004).

2.3. Human babesiosis in Europe and Asia

In Europe, *B. divergens, B. microti*, and *B. venatorum* are transmitted by the cattle tick *Ixodes ricinus*. Approximately 50 cases of *B. divergens* have been described. Most cases have been reported from France and Ireland but cases also have been reported from Croatia, Finland, Georgia, Norway, Poland, Portugal, Spain, Sweden and Turkey (Zintl et al., 2003; Hunfeld et al., 2008; Gray et al., 2010). *B. venatorum* was first described as EU-1 and cases have been reported in Austria, Germany, Italy and Sweden (Herwaldt et al., 2003; Hunfeld et al., 2008; Gray et al., 2010). Only three cases of *B. microti* have been reported in Europe (Germany and Poland) and two of these were asymptomatic infections (Hildebrandt et al., 2013; Welc-Falęciak et al., 2015).

In Asia, *B. venatorum* was first reported in northwestern China and subsequently found to be endemic in the northeastern province of Heilongjiang (Sun et al., 2014; Fang et al., 2015; Jiang et al., 2015). *Babesia crassa*-like infections have been discovered in the same province (Jia et al., 2018). *Babesia microti* cases have been reported in southwestern China along the Myanmar border, in Taiwan, and in Japan (Shih et al., 1997; Wei et al., 2001; Zhou et al., 2014, 2015). Another *Babesia* sp. causing human infection, XXB/Hang/Zhou, was recently described in southeastern China (Man et al., 2016). A case of babesiosis caused by KO-1 has been described in South Korea (Kim et al., 2007).

2.4. Human babesiosis in other parts of the world

Isolated cases of human babesiosis due to *B. microti* have been reported from Australia (Senanayake et al., 2012), Canada (Bullard et al., 2014), and Mexico (Peniche-Lara et al., 2018). Other cases have been reported in Cuba, Egypt, India, South America and South Africa but the precise *Babesia* sp. was not identified in any of these cases (Vannier and Krause, 2012).

2.5. Ecology and transmission of babesia infection

Babesiosis is a zoonotic disease that is transmitted by hard tick (ixodid) vectors from infected animal reservoirs. The tick vectors and reservoir hosts differ geographically for the same *Babesia* spp. and for different *Babesia* spp. (Table 1).

2.5.1. Babesia transmission in the United States

The primary reservoir hosts for *B. microti* are small rodents such as mice and voles but a large array of hosts are found worldwide, including ruminants, chipmunks, rats and shrews (Spielman et al., 1985). The primary tick vector is *I. scapularis*. 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 in order to mature to the next stage (Fig. 3). Newly hatched larvae ingest *Babesia* with a blood meal from an infected rodent in late summer and maintain the parasite to the nymphal stage. Nymphs transmit *B. microti* to rodents and humans in late spring, summer, and early autumn of the following year (Spielman et al., 1985). Adult *I. scapularis* may infrequently transmit *B. microti* to humans. They preferentially feed on white-tailed deer (*Odocoileus virginianus*) in the Northeast and northern Midwest. Deer do not become infected with *B. microti* but they amplify the tick population by providing a place for procreation and a blood meal that allows the female tick to lay eggs in the spring. The marked increase in the deer population during the past few decades is thought to be a major factor in the increase in the number of *I. scapularis*, with an attendant increase in the number of human *Ixodes*-transmitted infections, including babesiosis (Spielman et al., 1985; Diuk-Wasser et al., 2014). *Ixodes scapularis* transmits six other pathogens: *Anaplasma phagocytophilum, Borrelia burgdorferi, Borrelia miyamotoi, Borrelia myonii, Ehrlichia muris eauclairensis* and Powassan virus. *Ixodes scapularis* ticks, reservoir hosts, and humans may be infected simultaneously with two or more of these agents (Krause et al., 1996a; Holman et al., 2004; Swanson et al., 2006; Tokarz et al., 2010; Wormser and Pritt, 2015; Diuk-Wasser et al., 2016). Recent evidence suggests that *Dermacentor albipictus* is the vector of *B. duncani* and the reservoir host is the mule deer, *Odocoileus hemionus* (Swei et al., 2019).

The rise in *B. microti* tick-transmitted disease has been accompanied by an increase in *B. microti* cases transmitted through blood transfusion (Young and Krause, 2009; Herwaldt et al., 2011; Moritz et al., 2016). *Babesia microti* currently is the most common

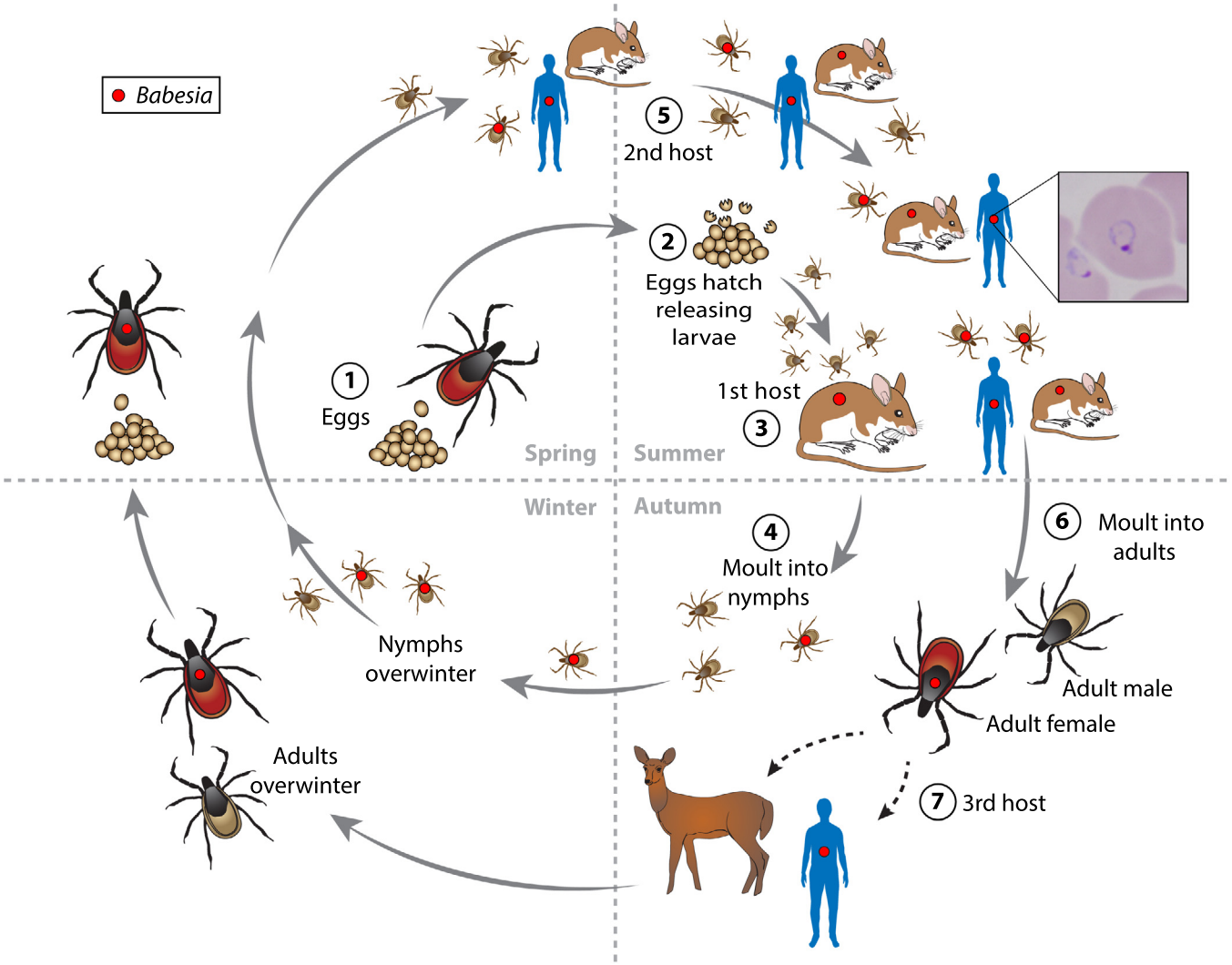

Fig. 3. Stages in the *Ixodes scapularis* tick life cycle and the transmission of *Babesia microti*. Female *I. scapularis* lay eggs in the spring that hatch in early summer and produce larvae (1 and 2). Larval *I. scapularis* ticks become infected with *B. microti* when they take a blood meal from infected white-footed mice (*Peromyscus leucopus*) or other small rodent hosts in late summer (3). Larvae moult into nymphs and overwinter (4). The following late spring, summer, and early autumn, infected nymphs transmit *B. microti* to uninfected mice or humans when they take a blood meal (5). In the autumn, nymphs moult into adults (6). Adults feed on white-tailed deer (*Odocoileus virginianus*) but rarely on humans (7). Adults overwinter and the females lay eggs in the early spring to complete the tick life cycle. White-tailed deer amplify the tick population by providing a breeding site for male and female ticks and a blood meal that allows female ticks sufficient protein to lay eggs in the spring. Deer do not become infected with *B. microti*. The inset shows a *B. microti* parasite ring form on a Giemsa-stained thin blood smear (adapted from New England Journal of Medicine, Vannier E., Krause P.J. Human babesiosis. 2012; 366: 2399. Copyright © (2019) Massachusetts Medical Society. Reprinted with permission).

pathogen transmitted through the blood supply in the United States and more than 200 cases have been reported (Herwaldt et al., 2011; Moritz et al., 2016). People who experience asymptomatic *B. microti* infection or who have asymptomatic infection following acute babesiosis may donate blood and unwittingly infect blood recipients (Krause et al., 1998; Herwaldt et al., 2011; Leiby et al., 2014; Moritz et al., 2016; Kumar et al., 2018) (Fig. 4). Three cases of blood transfusion transmission of *B. duncani* also have been described (Herwaldt et al., 2011; Bloch et al., 2012).

2.5.2. Babesia transmission in Europe and Asia

Babesia divergens occurs primarily in Europe and is transmitted by *I. ricinus* ticks with cattle as the primary reservoir hosts (Zintl et al., 2003). Interestingly, *I. ricinus* also serves as a reservoir host because *B. divergens* is transmitted by transovarial (and transstadial) transmission (Bonnet et al., 2007; Gray et al., 2010). Transovarial transmission occurs when a microorganism is passed from pregnant female ticks to their eggs so that larval, nymphal and adult stages are infected. Thus, an infection cycle exists without a mammalian reservoir host. Transstadial transmission occurs between life stages of the tick with the nymphal stage transmitting most infections (Fig. 3). Similar to *B. divergens*, *B. venatorum* is designated as a *Babesia* sensu stricto sp. and is transmitted both transstadially and transovarially by *I. ricinus* ticks. The primary reservoir for *B. venatorum* in Europe appears to be roe deer (Gray et al., 2010). An increase in the number of *I. ricinus* ticks may account for an increase in Lyme disease cases reported in parts of Europe, however there has been no reported increase in babesiosis cases. Expansion of the *I. ricinus* tick population is thought to be due to an increase in the roe deer population, deer and tick habitat change, climate change, and land management changes; similar to causes ascribed to the increase in *I. scapularis* populations in the US (Medlock et al., 2013). *Babesia venatorum* is endemic in northeastern China where it is thought to be transmitted by *I. persulcatus*. The *B. crassa*-like agent infects both *I. persulcatus* and *Haemaphysalis concinna* ticks and recently has been shown to infect humans (Jia et al., 2018). *Ixodes ovatis* has been implicated in transmission of *B. microti* in Japan. No case of blood transfusion transmission of *B. divergens* has been documented.

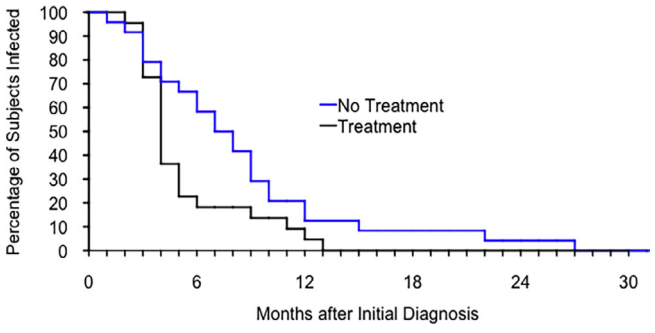

Fig. 4. Persistence of *Babesia microti* DNA in humans following acute babesiosis. Blood samples from patients experiencing acute babesiosis were tested for *B. microti* DNA using PCR every three months following the onset of infection until DNA was no longer detectable. One group ($n = 22$) with moderate to severe babesiosis was treated with clindamycin and quinine. A second group ($n = 24$) with mild babesiosis was not treated because the only treatment at the time was clindamycin and quinine, which is associated with numerous adverse side effects and immunocompetent patients experiencing mild infection resolved their infection without therapy. The subjects treated with clindamycin and quinine had a shorter duration of parasitemia as measured by PCR than the 24 untreated subjects ($P = 0.05$ by the log-rank test) (adapted from New England Journal of Medicine, Krause P.J., Spielman A.,Telford S.R. 3rd, Sikand V.K., McKay K., Christianson D., Pollack R.J., Brassard P., Magera J., Ryan R., Persing D.H. Persistent parasitemia after acute babesiosis. 1998; 339: 163. Copyright © (2019) Massachusetts Medical Society. Reprinted with permission).

3. Clinical manifestations

3.1. Babesia microti infection

Clinical manifestations of babesiosis range from asymptomatic infection to fulminating disease resulting in death (Ruebush et al., 1977a,b; Krause et al., 1996a, 2008; White et al., 1998; Hatcher et al., 2001; Joseph et al., 2011; Jiang et al., 2015). Following an incubation period of 1–6 weeks (usually 1 to 4 weeks) after tick bite or 1 week to 6 months (usually 1 to 9 weeks) after blood transfusion (Ruebush et al., 1981; Herwaldt et al., 2011), patients usually experience the gradual onset of malaise and fatigue, and then a combination of additional symptoms. The most common are intermittent fever as high as 40 °C (104 °F), fatigue, chills, sweats, anorexia, headache and myalgia (Ruebush et al., 1977a,b; Krause et al., 1996a, 2008; White et al., 1998; Hatcher et al., 2001; Joseph et al., 2011; Jiang et al., 2015; Mareedu et al., 2017). Less common symptoms include arthralgia, emotional liability and depression, hyperesthesia, neck stiffness, sore throat, nausea, abdominal pain, vomiting, conjunctival injection, photophobia, weight loss, shortness of breath and non-productive cough (Ruebush et al., 1977a,b; Sun et al., 1983; White et al., 1998; Hatcher et al., 2001; Jiang et al., 2015). Physical examination findings include fever, occasional mild to moderate splenomegaly, hepatomegaly, pallor, and/or jaundice (Ruebush et al., 1977a,b; Krause et al., 1996a; Joseph et al., 2011). Laboratory abnormalities include mild to moderately severe hemolytic anemia, an elevated reticulocyte count, thrombocytopenia, and elevated liver enzyme levels (Ruebush et al., 1977a,b; White et al., 1998; Joseph et al., 2011). Proteinuria and elevated blood urea nitrogen and creatinine may occur (Ruebush et al., 1977a,b; White et al., 1998).

Severe babesiosis usually is noted in immunocompromised patients, especially those with advanced age, neonatal prematurity, asplenia, HIV/AIDS, malignancy, immunosuppressive therapy, or cardiac, hematologic or liver comorbidities (White et al., 1998, Hatcher et al., 2001; Zintl et al., 2003; Hunfeld et al., 2008; Krause et al., 2008; Gray et al., 2010; Vannier and Krause, 2012). These patients are more susceptible to complications such as severe anemia, acute respiratory distress syndrome, disseminated intravascular coagulation, congestive heart failure, renal failure, coma, and hemophagocytic lymphohistiocytosis (Sun et al., 1983; Gordon et al., 1984; Hatcher et al., 2001; Krause et al., 2008). Anemia is commonly noted due to parasite-induced hemolysis and less commonly from autoimmune hemolytic anemia (White et al., 1998; Woolley et al., 2017). Interestingly, splenic rupture occurs more commonly in younger and healthier patients (Patel et al., 2019). Complications are common in hospitalized patients, including death in 3–9% of such cases. Among those experiencing severe babesiosis and who are immunocompromised or who acquire the infection through blood transfusion, the fatality rate can be as high as 20% (Krause et al., 2008; Herwaldt et al., 2011). Severe babesial illness usually lasts a few weeks to several months. Persistent asymptomatic parasitemia lasting for several months is common following acute babesiosis. Relapse of illness in previously healthy adults is very uncommon but may occur as long as 27 months after initial illness (Krause et al., 1998; Raffalli and Wormser, 2016) (Fig. 4). Prolonged symptomatic relapsing illness is sometimes observed in highly immunocompromised patients and can occur despite standard antibiotic therapy (Krause et al., 2008; Raffalli and Wormser, 2016).

3.2. Babesia divergens infection

Babesia divergens infections in humans have occurred almost exclusively in Europe, although four *B. divergens*-like infections

have been described in the United States (Herwaldt et al., 2004). Almost all of the *B. divergens* cases have occurred in asplenic individuals and have been severe, many with a fulminant course. In some reports, parasitemia has been as high as 80% and more than a third of the cases died. Six cases of *B. divergens* have been described in patients who were not asplenic, although two of them had hyposplenism secondary to comorbid conditions (Haapasalo et al., 2010; O'Connell et al., 2017) and one was an elderly patient with probable malignancy (Asensia et al., 2018). The other three were apparently immune intact (Olmeda et al., 1997; Martinot et al., 2011; Gonzalez et al., 2014). Recent more aggressive diagnostic and therapeutic management, including rapid institution of intravenous antibiotic and exchange transfusion, have resulted in improved outcomes (Zintl et al., 2003; Hunfeld et al., 2008; Gray et al., 2010; Hildebrandt, et al., 2013).

3.3. Babesia venatorum and B. duncani infections

Sporadic cases of *B. venatorum* were first described in Europe with a clinical course similar to that of *B. microti*, although infection in immunosuppressed patients may be severe. Subsequent cases of *B. venatorum* in China have also had a similar, although milder course. Less than 20 *B. duncani* cases have been described and clinical manifestations were similar to those of *B. microti*. Several had severe illness and one patient died.

4. Pathogenesis and immune mechanisms

Babesia infect erythrocytes and multiply into two to four daughter cells (merozoites) that are then intermittently released to infect new erythrocytes (Rudzinska, 1981). The release of merozoites and eventual erythrocyte lysis is associated with the symptoms and complications of the infection, including hemolytic anemia, jaundice, hemoglobinemia, obstruction of renal arterioles, and renal insufficiency (Rudzinska, 1981; Clark et al., 2004). In contrast to *Babesia* spp. merozoites that are release intermittently, *Plasmodium* spp. merozoites are released all at once (synchrony). The repetitive cycles of febrile episodes noted with malaria, but not babesiosis, may be explained by the difference in synchronous and non-synchronous replication (Krause et al., 2007). In addition to erythrocyte lysis and metabolic alterations induced by infection, two other mechanisms are hypothesized to contribute to clinical manifestations and complications, namely excessive proinflammatory cytokine production and obstruction of blood vessels due to erythrocyte cytoadherence (Clark and Jacobson, 1998; Hemmer et al., 2000; Allred, 2003; Krause et al., 2007). Although cytoadherence appears to play a role in the pathogenesis of disease complications in cattle infected with *B. bovis*, it has yet to be demonstrated in human babesial infection (Hutchings et al., 2007; Krause et al., 2007). A report of fatal human *B. microti* infection with cerebral involvement was not associated with erythrocyte adherence or vascular occlusion within the brain (Clark et al., 2006). The release of proinflammatory cytokines in patients with babesiosis may have multiple effects with excessive release of downstream mediators (such as nitric oxide) which kill parasites. They also may cause direct cellular damage, as well as vascular leakage that may lead to adult respiratory distress syndrome, hypotension, and shock (Clark and Jacobson, 1998; Clark et al., 2004, 2006; Cornillot et al., 2012).

Both innate and adaptive immune mechanisms limit the severity of babesial infections (Hemmer et al., 2000; Vannier et al., 2004; Terkawi et al., 2015; Elton et al., 2019). The spleen is a critical immune organ for blood-borne infections, especially intraerythrocytic infections such as babesiosis. It acts immediately to limit when the sieve-like structure of splenic venules trap *Babesia*-infected erythrocytes and allow macrophages to ingest and kill these erythrocytes and their contents (Rosner et al., 1984; Cullen and Levine, 1987; Wright et al., 1989; Vannier and Krause, 2012). The spleen also contains B and T lymphocytes that help control infection later in the course of illness. Asplenia often results in fulminant illness and death with both *B. microti* and *B. divergens* infections. A series of patients who had severe immunosuppression, including impaired antibody production due to B cell lymphoma, Retuximab therapy and/or asplenia, had difficulty in clearing infection despite repeated courses of antibiotics (Krause et al., 2008). Age is an important factor in host defense against babesial disease in animals and humans. Not only are most clinically apparent cases reported in adults, those over 50 years of age are more susceptible to severe disease. The majority of elderly patients experience mild to moderate illness, however (Ruebush et al., 1977a,b; Krause et al., 1991; White et al., 1998; Menis et al., 2015). Data from a murine model of babesiosis have suggested that resistance to *B. microti* infection conferred by the adaptive immune system is genetically determined and associated with age (Vannier et al., 2004).

5. Diagnosis

Babesiosis should be considered in anyone who has characteristic babesial symptoms and has lived in or traveled to an endemic area in the late spring to early autumn, or has received a blood transfusion in the previous 6 months (Vannier and Krause, 2012). Fever is the most common finding on physical examination. Abdominal tenderness of the upper left quadrant suggests splenomegaly. Jaundice may be due to hemolysis and petechiae to disseminated intravascular coagulopathy (DIC). An expanding, erythematous skin lesion may be due to concurrent Lyme disease (Krause et al., 1996a; White et al., 1998; Joseph et al., 2011; Diuk-Wasser et al., 2016). Screening laboratory tests that help support the diagnosis include a complete blood count (CBC) that shows low hemoglobin and hematocrit, an elevated reticulocyte count, and/or a low platelet count (White et al., 1998; Joseph et al., 2011). The leukocyte count is usually normal-to-slightly decreased; neutropenia may occur in infants and adults. Elevated lactate dehydrogenase levels are common due to hemolytic anemia. Liver enzymes (alkaline phosphatase, aspartate and alanine aminotransferases) and bilirubin are elevated in severe disease (Hatcher et al., 2001). Urinalysis may reveal hemoglobinuria, hematuria, and excess urobilinogen. Elevated levels of blood urea nitrogen and serum creatinine may occur due to renal compromise.

A diagnosis of babesiosis can be confirmed by microscopic detection of parasites within red blood cells on Giemsa-stained or Wright-stained thin blood smears, as shown in in Fig. 3 and the graphical abstract (Healy and Ruebush, 1980). Thick smears may help detect *Babesia* spp. when parasitemia is low but *Babesia* may be overlooked using this approach. *Babesia* trophozoites can be incorrectly identified as early-stage *Plasmodium falciparum* trophozoites. Merozoites arranged in a tetrad ("Maltese cross") are pathognomonic for *Babesia* infection but are rarely noted. PCR is more sensitive than a blood smear for detection of *Babesia* (Krause et al., 1996b). Real-time PCR assays can detect as few as 0.1 to 10 parasites per microliter of blood and allow speciation of *Babesia* (Bloch et al., 2013; Wang et al., 2015; Wilson et al., 2015; Grabias et al., 2018). A single positive *Babesia* serological test cannot distinguish active from past infection, although a *B. microti* antibody titer or $\geq$1:1024 or the presence of IgM antibody suggest recent infection (Ruebush et al., 1977a,b; Krause et al., 1996c; Levin et al., 2016). A four-fold increase in antibody titer in acute and convalescent sera is confirmatory evidence of babesial infection.

6. Treatment

6.1. Babesia microti infection

Antibiotic treatment of babesiosis is generally very effective and consists of atovaquone and azithromycin (Krause et al., 2000; Kletsova et al., 2017). An alternative regimen is clindamycin and quinine but there are numerous side effects associated with this combination. Antibiotic therapy is usually given for 7–10 days. Immunocompromised patients may not respond adequately to standard antibiotic therapy and may require red blood cell exchange transfusion, which consists of removing a patient's red blood cells and replacing them with donor red blood cells. Exchange transfusion is warranted for patients with babesiosis who have a parasitemia ≥10 percent, severe hemolysis (hemoglobin <10 g/dL), or pulmonary, liver or renal impairment (Spaete et al., 2009; Saifee et al., 2016). Either partial or complete exchange transfusion may be carried out depending on the severity of disease. Patients who are highly immunocompromised may experience persistent and relapsing infection, and may require more prolonged antibiotic therapy (Krause et al., 2008). Treatment failure has been observed with atovaquone plus azithromycin and with clindamycin plus quinine (Krause et al., 2008; Wormser et al., 2010; Simon et al., 2017). Alternative antibiotic combinations have been used successfully but there have been no controlled trials to confirm their efficacy (Krause et al., 2008).

6.2. Babesia divergens, B. duncani infection, B. venatorum

Aggressive management is recommended for *B. divergens* infections because most cases have occurred in asplenic individuals who have experienced severe disease, often with a very rapid onset. Treatment consists of clindamycin (given intravenously) plus quinine and early consideration of red blood cell exchange transfusion (Hunfeld et al., 2008; Gray et al., 2010). *Babesia duncani* has been treated successfully with clindamycin and quinine. *Babesia venatorum* is treated in a similar manner to *B. microti.*

7. Prevention

7.1. General measures

Approaches to curtail *B. microti* transmission include avoiding areas during the transmission season (May through September in the United States) where ticks, deer, and mice are common. This is especially important for people with immune deficiencies including asplenia, B cell lymphoma, HIV/AIDS, organ transplant recipients and those on major immunosuppressant drugs such as Retuximab (Desforges and Quimby, 1976; Vannier and Krause, 2012). Other personal protective measures for individuals who travel into the foliage of endemic areas consist of the use of clothing that covers the lower part of the body and is sprayed or impregnated with permethrin (Permanone) (Hayes and Piesman, 2003; Finch et al., 2014). A search for ticks can be carried out and the ticks removed as soon as possible using tweezers (Finch et al., 2014). Recommended landscape management approaches include keeping grass mowed, clearing leaf litter, and spraying property with an acaricide where tick density is high (Connally et al., 2009; Finch et al., 2014). Reduction of deer populations in certain endemic areas such as on islands, has been shown to be effective in reducing the incidence of Lyme disease and presumably would do the same for babesiosis (Wilson et al., 1988; Kilpatrick et al., 2014). Effective *B. bovis* and *B. bigemina* vaccines have been developed for use in cattle and a *B. rossi* vaccine for dogs (Schetters et al., 2009), but no human *Babesia* vaccine has been developed. The optimal approach would be a vaccine that protects against several *Ixodes*-transmitted pathogens based on multiple microbial recombinant antigens or tick salivary antigens (an "anti-tick" vaccine), however, the prospect for near-term development of such a vaccine is remote. It is important to recognize that none of these measures will curtail the continued expansion of *B. microti* into non-endemic areas. As with Lyme disease, the limit of expansion for human babesiosis is currently unknown, but it may ultimately coincide with the expanding range of *Ixodes* ticks (Hoen et al., 2009).

7.2. Protecting the blood supply

Transmission of *B. microti* through blood transfusion is a serious public health threat in the United States and improved preventive measures are needed. Currently, people living in endemic areas are prevented from giving blood if they have a history of babesiosis. This approach is inadequate because many infections are asymptomatic or are not diagnosed and result in persistent, asymptomatic infections that remain undetected despite such screening (Krause et al., 1998; Leiby et al., 2014; Moritz et al., 2016). Laboratory screening of blood donors for pathogen exposure is a common preventative measure. A combination of screening for *B. microti* antibody and *B. microti* DNA has been shown to successfully identify and remove potentially infectious donations from the blood supply (Young et al., 2012; Moritz et al., 2016). These methods could be used in selected endemic regions to decrease the risk of transfusion-transmitted infections (Kumar et al., 2018). Pathogen inactivation methods have been used successfully to prevent transfusion-transmitted *P. falciparum* malaria in humans and reduce *B. microti* parasitemia in a hamster transfusion model (Allain et al., 2016; Tonnetti et al., 2017).

8. Summary

Human babesiosis is a worldwide problem and presents a significant health burden in areas where it is endemic. Several aspects of the disease are especially concerning. The incidence and geographic range of disease is increasing globally. The mortality rate is high among immunocompromised hosts and those with certain comorbidities. *Babesia microti* is the most common pathogen transmitted through blood transfusion in the United States and approximately one-fifth of those cases result in death. Current antibiotic therapy is effective in most cases but immunocompromised patients often require more aggressive therapy and sometimes more prolonged therapy. Improved preventive measures are needed.

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