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departure so that any untoward reactions can be detected before travel and therapeutic antimalarial blood concentrations will be present if and when any infections develop (Table 231-8). Antimalarial prophy laxis should continue for 4 weeks after the traveler has left the endemic area, except if atovaquone-proguanil or primaquine has been taken; these drugs have significant activities against the liver stage of the infection (causal prophylaxis) and can be discontinued 1 week after departure from the endemic area. If suspected malaria develops while a traveler is abroad, obtaining a reliable diagnosis and antimalarial treat ment locally is a top priority. Presumptive self-treatment for malaria with atovaquone-proguanil (for 3 consecutive days) or one of the artemisinin-based combinations can be considered under special cir cumstances; medical advice on self-treatment should be sought before departure for malaria-endemic areas and as soon as possible after illness begins. Every effort should be made to confirm the diagnosis. Atovaquone-proguanil (3.75/1.5 mg/kg or 250/100 mg, daily adult dose) is a fixed-combination, once-daily prophylactic agent that is very well tolerated by adults and children. This combination is effective against all types of malaria, including multidrug-resistant falciparum malaria. Atovaquone-proguanil is best taken with food or a milky drink to optimize absorption. It is not recommended if the estimated glomerular filtration rate is <30 mL/min. There are insufficient data on safety for prophylaxis in pregnancy. Mefloquine (250 mg of salt weekly, adult dose) has been widely used for malarial prophylaxis because it is usually effective against multidrug-resistant falciparum malaria and is reasonably well toler ated. Mefloquine has been associated with rare episodes of psychosis and seizures at prophylactic doses; these reactions are more frequent at the higher doses used for treatment. More common side effects with prophylactic mefloquine include mild nausea, dizziness, fuzzy think ing, disturbed sleep patterns, vivid dreams, dysphoria, and malaise. Mefloquine is contraindicated for use by travelers with known hyper sensitivity and by persons with active or recent depression, anxiety disorder, psychosis, schizophrenia, another major psychiatric disorder, or seizures; it is not recommended for persons with cardiac conduc tion abnormalities, although the evidence that it is cardiotoxic is very weak. Daily administration of doxycycline (100 mg daily, adult dose) is an effective alternative to atovaquone-proguanil or mefloquine. Doxy cycline is generally well tolerated but may cause vulvovaginal thrush, diarrhea, and photosensitivity and is not recommended for prophylaxis in children <8 years old or pregnant women, although evidence that it is harmful in children is lacking. Chloroquine can no longer be relied upon to prevent P. falciparum infections but is still used to prevent and treat malaria due to the other human Plasmodium species and for P. falciparum malaria in Central American countries west and north of the Panama Canal and in Caribbean countries. Chloroquine-resistant P. vivax has been reported from parts of eastern Asia, Oceania, and Central and South America. High-level resistance in P. vivax is prevalent in Oceania and Indonesia. Chloroquine is generally well tolerated, although some patients cannot take it because of malaise, headache, visual symptoms (due to revers ible

keratopathy), gastrointestinal intolerance, alopecia, or pruritus. Chloroquine is considered safe in pregnancy. With chronic administra tion for >5 years, a characteristic dose-related retinopathy may develop, but this condition is rare at the doses used for antimalarial prophylaxis. Idiosyncratic or allergic reactions are also rare. Skeletal and/or cardiac myopathy is a potential problem with protracted prophylactic use, although it is more likely to occur at the high doses used in the treat ment of rheumatoid arthritis. Neuropsychiatric reactions and skin rashes are unusual. Amodiaquine should not be used for weekly pro phylaxis because continuous weekly use is associated with a high risk of agranulocytosis (~1 person in 2000) and hepatotoxicity (~1 person in 16,000). Chloroquine, amodiaquine, and piperaquine all cause moder ate electrocardiograph QT prolongation but have not been associated with ventricular arrhythmias at therapeutic doses. Primaquine (0.5 mg of base/kg or a daily adult dose of 30 mg taken with food), an 8-aminoquinoline compound, has proved safe and effec tive in the prevention of drug-resistant falciparum and vivax malaria in adults. Primaquine can be considered for adults (with the exception

of pregnant women) who are intolerant to other recommended drugs. Abdominal pain can be prevented by taking primaquine with food. G6PD deficiency must be excluded before primaquine is prescribed. In the past, the dihydrofolate reductase inhibitors pyrimethamine and proguanil (chloroguanide) were administered widely, but the rapid selection of resistance in both P. falciparum and P. vivax has limited their use. Whereas antimalarial quinolines such as chloroquine (a 4-aminoquinoline) act only on the erythrocyte stage of parasitic development, the dihydrofolate reductase inhibitors (as well as ato vaquone and primaquine) also inhibit preerythrocytic growth in the liver (causal prophylaxis) and development in the mosquito (sporon tocidal activity). Proguanil is safe and well tolerated, although mouth ulceration occurs in ~8% of persons using this drug; it is considered safe for antimalarial prophylaxis in pregnancy. Prophylactic use of the combination of SP or amodiaquine is not recommended for weekly administration because of an unacceptable incidence of severe toxicity, principally exfoliative dermatitis and other skin rashes (SP) (incidence, 1 in 7000; fatal reactions, 1 in 18,000), agranulocytosis (amodiaquine), hepatitis, and pulmonary eosinophilia (both drugs).

Because of the increasing spread and intensity of antimalarial drug resistance, the Centers for Disease Control and Prevention (CDC) rec ommends that travelers and their providers consider their destination, type of travel, and current medications and health risks when choosing antimalarial chemoprophylaxis. There is an increasingly appreciated problem of falsified and substandard antimalarial drugs (and other medicines) on the shelves of pharmacies in Southeast Asia and subSaharan Africa; hence, travelers should purchase their preventive drugs from a reputable source before going to a malarious country. Consulta tion for the evaluation of prophylaxis failures or treatment of malaria can be obtained from state and local health departments and the CDC Malaria Hotline (770) 488-7788 or (855) 856-4713 [toll free]) or the CDC Emergency Operations Center (770-488-7100 [after hours]). CHAPTER 232 Acknowledgment The authors gratefully acknowledge the substantial contributions of Joel G. Breman, MD, to this chapter in the previous editions. Babesiosis ■ ■FURTHER READING World Health Organization: WHO guidelines for malaria. October 16, 2023. Available at: https://www.who.int/teams/globalmalaria-programme/guidelines-for-malaria. Accessed March 1, 2024. Edouard Vannier, Jeffrey A. Gelfand

Babesiosis Babesiosis is an emerging infectious disease caused by protozoan para sites of the genus Babesia that invade and eventually lyse red blood cells (RBCs). Most cases occur in the

United States during the summer months and are caused by Babesia microti, a species typically found in small rodents and transmitted by the deer tick, Ixodes scapularis. Symptoms are those of a flu-like illness. For most patients, a single standard course of atovaquone plus azithromycin is sufficient to achieve cure. Highly immu nocompromised patients and asplenic individuals are at risk of persistent infection and should be treated for a longer duration. Adjunct red cell exchange can be useful for severe cases. In the absence of vaccine and chemoprophylaxis, persons at risk of severe babesiosis should minimize their exposure to ticks and, if possible, avoid endemic areas. ■ ■ETIOLOGY, EPIDEMIOLOGY, AND

MODES OF TRANSMISSION A few Babesia species have been implicated as etiologic agents of human babesiosis. These species use wild or domesticated mammals

as reservoir hosts and are maintained in their enzootic cycle by ticks. Humans are incidental, dead-end hosts. Most cases are reported from across the Northern Hemisphere; the predominant etiologic agent varies by continent.

United States • GEOGRAPHIC DISTRIBUTION Most cases (>95%) are caused by B. microti and are reported from the Northeast (Massachusetts, Rhode Island, Connecticut, Vermont, New Hampshire, Maine, New York, New Jersey) and the upper Midwest (Minnesota, Wisconsin) (Fig. 232-1). Other Babesia species seldom cause disease. Symptomatic infection with Babesia duncani and B. duncani–type organisms has been reported from Washington State, Oregon, and California. Symptomatic infection with Babesia divergens–like organisms has been documented in the central states of Arkansas, Missouri, Michigan, and Kentucky and also in Washington State and Pennsylvania. INCIDENCE Cases are reported weekly by state health departments to the Centers for Disease Control and Prevention (CDC) via the National Notifiable Diseases Surveillance System. In 2023, more than 3200 cases were reported from 33 of the 40 states in which babesiosis is notifiable. In 2011, when babesiosis became a nationally notifiable disease, 1126 cases were reported to the CDC. The increase in incidence over time is best explained by a greater density of ticks in highly endemic areas and by the northward expansion of these ticks. Although B. microti and Borrelia burgdorferi (the agent of Lyme disease; Chap. 191) are transmitted by the same tick species, the deer tick I. scapularis, the geographic expansion of babesiosis has lagged behind that of Lyme disease. This delay likely reflects the poor ecologic fitness of B. microti compared with that of B. burgdorferi and is consistent with the observation that B. burgdorferi helps maintain B. microti in their shared enzootic cycle. Other factors contributing to the rise in the incidence of babesiosis include greater exposure to ticks due to forest fragmentation in suburban areas and increased leisure activities in grassy or wooded areas. PART 5 Infectious Diseases I. ricinus B. divergens B. microti I. scapularis B. duncani FIGURE 232-1 Geographic distribution of human babesiosis and associated tick vectors. 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. Circles depict single cases except in six locations (Colombia, Mexico, Montenegro, Poland, and the provinces of Gansu and Shandong in China) where all patients were diagnosed at one hospital or identified via survey in one location. Colors distinguish the etiologic agents: red for Babesia microti, orange for B. duncani, blue for B. divergens and B. divergens–like, green for B. venatorum, pink for B. crassa–like, brown for B. bovis and B. bigemina, and black for B. motasi–like. White circles depict cases caused by uncharacterized Babesia isolates or by isolates for which the full sequence of the 18S rRNA gene was not available

or ruled out all of the Babesia species listed above. Asymptomatic infections and cases of travel-associated babesiosis are omitted.

MODES OF TRANSMISSION • Tick Bite B. microti is acquired primarily during the blood meal of an I. scapularis tick. Less than one-half (~45%) of patients recall a tick bite within the 8 weeks prior to symptom onset. Both nymphs and adult ticks can transmit B. microti; tick larvae are not infected because B. microti is not transmitted transovarially. Most cases (~90%) present from June through August because nymphs—the primary vector—are active from late spring to early summer. Patients who present in the fall may have acquired B. microti from an adult female tick. B. duncani and B. divergens–like organisms are thought to be transmitted by Dermacentor albipictus and Ixodes dentatus ticks, respectively. Blood Transfusion More than 300 cases of transfusion-transmitted babesiosis (TTB) caused by B. microti have been reported. Most cases involve packed RBCs; a few have been attributed to frozen-deglycerolized RBCs and whole blood–derived platelets contaminated with RBCs but none to apheresis platelets. At the time of transfusion, the age of the refrigerated RBC units has ranged from 4 to 42 days, indicating that B. microti remains viable throughout the RBC unit's shelf life. Acellular blood components (plasma, cryoprecipitate) have not been implicated. TTB has occurred year-round because B. microti can persist for more than a year in untreated asymptomatic carriers. Given the seasonality of tick-borne babesiosis, two-thirds of the donations implicated in TTB cases have been obtained from June through October. Like that of tickborne babesiosis, the incidence of TTB sharply increased during the first two decades of the millennium. In May 2020, the American Red Cross (ARC) began to test all blood donations collected in the 15 jurisdictions that account for 99% of tick-borne babesiosis cases and 95% of TTB cases. During the following 13 months, no suspected TTB cases were reported to the ARC. In contrast, from 2010 to 2017, B. microti– positive donations were linked to 81 TTB cases (~10 cases per year). Screening of the blood supply relies on the amplification of parasite 18S rRNA gene transcripts. In addition to B. microti, the Procleix Babesia B. venatorum & B. crassa I. persulcatus I. ovatus B. microti

Assay detects B. duncani and B. divergens, which have been implicated in a handful of TTB cases. The assay is exquisitely sensitive; the 95% limit of detection is 3 parasites per mL of blood for B. microti and B. duncani, and 2 parasites per mL of blood for B. divergens. Vertical Transmission Passage of B. microti across the placenta has been documented but is rare. Symptoms typically develop during the third to the sixth week of life and often consist of fever accompanied by pallor and lethargy. Parasitemia at presentation has ranged from 2% to 5%. Both the neonate and the mother typically are seropositive for

B. microti IgG antibody. Most cases of neonatal babesiosis, however, are acquired through blood transfusion or tick bite. Infants (<1 year of age) account for <1% of the annual number of cases of babesiosis reported to the CDC. Solid Organ Transplantation This unusual mode of transmission has been highlighted in a single case report. Two patients received a diagnosis of babesiosis 8 weeks after transplantation of a kidney allograft obtained from a single donor who had received multiple transfusions shortly before his death. Corneas from the deceased donor were transplanted, but neither recipient was infected with B. microti; this outcome sug gests that RBCs that had remained in the vasculature or fluids of the donated kidneys were the source of B. microti. Risk Factors Most patients (~80%) who present with symptoms of babesiosis are ≥50 years. Those who are admitted to a hospital are a decade older (median age, 68 years) than those who are not (median age, 59

years). Aside from tick exposure and advanced age, major risk factors for severe babesiosis include asplenia and immunosuppression. Asplenia can be congenital, functional (e.g., due to celiac disease or hemoglobinopathies such as sickle cell disease and thalassemia), or acquired (due to splenectomy). Immunosuppression often is iatro genic and associated with conditions such as autoimmune disorders, chronic inflammatory disorders, malignancies, or transplantation. Immunosuppression can be inherent in comorbidities such as X-linked agammaglobulinemia, common variable hypogammaglobulinemia, and HIV/AIDS. Risk factors for TTB include conditions that require transfusion of blood components, particularly RBCs. Outside the United States Travel-associated babesiosis may become more common if, as anticipated, Babesia species continue to emerge worldwide (Fig. 232-1). EUROPE More than 40 cases have been attributed to B. divergens since the index case was reported from Croatia in 1957. The infection is rarely diagnosed in immunocompetent individuals; most patients lack a spleen or have functional hyposplenism. Most cases occur in France and Ireland, particularly in regions with cattle farms. B. divergens, a parasite of cattle, is transmitted by the castor bean tick Ixodes ricinus. Other Babesia species rarely cause disease. B. divergens–like parasites have been implicated in 1 case on the Canary Islands and in another in western France. Five cases caused by Babesia venatorum have been reported from Italy, Austria, Germany, and Sweden. Two cases of infection with Babesia crassa–like organisms have been reported from Slovenia and western France. All 9 patients had been splenectomized. In Germany, a normosplenic patient with acute myeloid leukemia presumably acquired B. microti during the transfusion of whole blood–derived platelets. In eastern Poland, mild babesiosis caused by B. microti has occurred in normosplenic patients. I. ricinus is the vector for B. microti and B. venatorum and the presumed vector for B. divergens–like parasites. Haemaphysalis concinna is the likely vec tor for B. crassa–like organisms. B. microti is found in small rodents, B. venatorum in roe deer, and B. crassa in sheep. Rabbits are suspected reservoirs for B. divergens–like parasites. ASIA B. microti was recognized as a human pathogen in Taiwan in the late 1990s. In the past decade, babesiosis has gained the status of emerging infectious disease in mainland China. In the northeastern province of Heilongjiang, B. venatorum and B. crassa–like organisms have caused mild disease in immunocompetent individuals, whereas antibodies specific for B. microti have been detected in blood donors. The taiga tick Ixodes persulcatus is a competent vector for B. microti

and the presumed vector for B. venatorum. In this province, B. crassa– like organisms are found in I. persulcatus and H. concinna ticks. A case of B. venatorum infection was documented in a child residing in the northwestern Xinjiang Autonomous Region. Several cases of B. microti infection have been reported from southern China, mostly from Yunnan; two of the patients were co-infected with Plasmodium species, one with P. falciparum and the other with P. vivax.

The single case of babesiosis reported from Japan was acquired through blood transfusion and was caused by a B. microti organism that defines the Kobe lineage. Two cases have been reported from South Korea; both occurred in splenectomized individuals and were caused by Babesia motasi–like organisms, which are parasites of sheep and goats. In one case, Haemaphysalis longicornis was the presumed vector. REMAINDER OF THE WORLD Three cases of babesiosis caused by B. microti have been reported from Canada: two from southern Mani toba and one from southern Nova Scotia. Asymptomatic B. microti infection has been detected in a few blood donors from southwestern Ontario. Babesiosis is a reportable disease in Manitoba and Quebec. In Yucatan, Mexico, four cases of febrile illness have been attributed to B. microti. Evidence that Babesia bovis and Babesia bigemina may cause human illness has come from Uraba, a region of Colombia where cattle

ranching is important and malaria is endemic. In west ern India, the death of a young, splenectomized farmer was caused by a novel Babesia species. A fatal case of B. microti infection has been reported from New South Wales, Australia; the causative agent was likely imported. ■ ■CLINICAL MANIFESTATIONS CHAPTER 232 United States • B. MICROTI INFECTION Symptoms typically appear 1–4 weeks after the bite of an infected tick but 3–7 weeks (median, 37 days; range, 11–176 days) after transfusion of contami nated blood components. Patients experience a gradual onset of fatigue with or without malaise that is followed within days by fever and one or more of the following: chills, night sweats, headache, myalgia, and anorexia. Fever is persistent or intermittent and has reached 40.9°C (105.6°F). Less common symptoms include arthralgia, nausea, dry cough, neck stiffness, emotional lability, and sore throat. Diarrhea, vomiting, abdominal pain, and joint swelling are rare. Dark urine and jaundice raise the suspicion of severe hemolytic anemia and may be accompanied by shortness of breath. Babesiosis On physical examination, fever is the salient feature. The skin may be pale or yellowish. A focal red rash, if present, denotes the site of the tick bite; an erythema migrans rash (Fig. A1-8) signifies concur rent Lyme disease (Chap. 191) or southern tick-associated rash illness (STARI) (Chap. 190). Ecchymoses and petechiae are rare. Examination of the eyes may be remarkable for scleral icterus, which is consistent with severe hemolysis. Retinopathy with splinter hemorrhages and reti nal infarcts are rare. Tenderness of the abdominal upper left quadrant suggests splenomegaly, which may be accompanied by hepatomegaly. Left-sided abdominal pain raises suspicion of splenic infarction or splenic rupture. Unexplained hypotension accompanied by tachycardia reinforces suspicion of splenic rupture. Splenic infarction and subcap sular hematoma can occur in the absence of splenic rupture. Splenic infarction and splenic rupture are confirmed by CT. Splenic infarcts appear as wedge-shaped hypodense lesions. A hyperdense fluid sur rounding the spleen is consistent with hemoperitoneum caused by splenic rupture. Severe babesiosis requires hospital admission. The median length of hospital stay is 4 days (interquartile range, 3–7). Severe babesiosis can be accompanied by one or several complications. The leading compli cation is acute renal failure (20%). The second most common compli cation is acute respiratory failure (7%). Less common complications include supraventricular arrhythmia, heart failure, disseminated intra vascular coagulation, and shock. At least one transfusion of red blood cells is given to one of five patients hospitalized for babesiosis. Patients diagnosed >7 days after symptom onset are predisposed to severe complicated babesiosis, which has been defined as an illness requir ing admission to an intensive care unit (ICU); an illness complicated

by acute respiratory distress syndrome, heart failure or shock; or an illness requiring dialysis, intubation or RBC exchange. Among clini cal features, diarrhea and nausea or vomiting are strong predictors of severe babesiosis as just defined. Asplenia and autoimmune disorders predispose to severe disease, but underlying cardiac conditions do not. Concurrent Lyme disease does not decrease the risk of severe disease but has been associated with a lower risk for hospitalization; the impli cation is that a diagnosis of babesiosis should be considered in any patient diagnosed with Lyme disease.

Despite therapy, babesiosis can be fatal. Prior to the turn of the mil lennium, when clindamycin plus quinine was the regimen of choice for treatment of babesiosis, fatality rates ranging from 5% to 9% were reported. Since atovaquone plus azithromycin has become the first-line therapy, a fatal outcome is rare. Of the 7612 cases of babesiosis reported to the CDC in 2011–2015, 46 (0.6%) ended in death. Death is more frequent among those ≥65 years of age. A review of claims for

10,305 Medicare recipients who were diagnosed with babesiosis between 2006 and 2013 revealed that 1% had died within 30 days. Among those admitted to a hospital, the fatality rate was 3%. Fatality is high in immunocompromised patients (~20%) and those with splenic rupture or splenic infarction (6%). OTHER BABESIA INFECTIONS The eight documented cases of B. duncani infection reported in the United States were moderate to severe; one patient died. Symptoms were similar to those evoked by B. microti. All seven patients infected with B. divergens–like organisms had been splenectomized and experienced a severe illness that required hospi talization; three died. Global Considerations Most cases of B. divergens infection in Europe have occurred in individuals who lack a spleen or have func tional hyposplenism. Symptoms develop suddenly and consist of fever (>41°C [>105.8°F]), headache, lumbar or abdominal pain, and dark urine. Jaundice and hemoglobinuria are common. Without immediate therapy, including immediate red cell exchange, patients often develop renal failure with or without acute respiratory distress or failure. In spleen-intact individuals, B. divergens infection typically evokes a mild illness. All 5 patients infected with B. venatorum in Europe had been splenectomized; their illness ranged from mild to severe, and none died. The 32 cases of B. venatorum infection reported from northeastern China occurred in spleen-intact residents. Symptoms were similar to those evoked by B. microti, although chills were rare. Seven patients were hospitalized for intermittent fever as high as 40°C. Only 4 patients were treated with clindamycin (without quinine); all 32 patients recovered. Cases of B. crassa–like infection reported from northeastern China also occurred in spleen-intact residents. Fever, fatigue, and myalgia were less common than among patients infected with B. microti, but headache was as common and nausea or vomiting more common. No patient was admitted to a hospital. Only 3 of the 31 patients were given clindamycin (without quinine); none died. In Europe, 2 cases of B. crassa–like infection occurred in splenectomized individuals and were severe. Neither ended in death, although 1 patient required intensive care. Cases of B. motasi–like infection in South Korea were severe; 1 patient died but the other recovered following clindamycin monotherapy. PART 5 Infectious Diseases ■ ■PATHOGENESIS Anemia RBC debris generated by hemolysis may accumulate in the kidney vasculature and cause renal failure. Free hemoglobin is rapidly complexed by haptoglobin. Once haptoglobin is depleted, the heme group is oxidized, released from hemoglobin, and complexed by hemopexin. Excessive hemolysis results in excess free hemoglobin, which scavenges and consumes nitric oxide, leading to thrombus formation and vascular inflammation. RBC lysis in small capillaries of the spleen may trigger localized necrosis, leading to splenic infarc tion. Exposed to oxidative stress, RBCs become poorly deformable and are filtered out by splenic macrophages as they attempt to pass through the red pulp. Erythrophagocytosis, along with the mounting of an immune response, contributes to splenomegaly and splenic

rupture. Massive phagocytosis of RBCs, platelets, and white blood cells has led to hemophagocytic lymphohistiocytosis, a fatal condi tion. Persistent anemia, despite resolution of infection, has been attributed to autoantibodies that tag RBCs for clearance and may activate the complement system. Inflammation Fever, chills, and sweats likely result from the systemic inflammatory response triggered by RBC lysis. Excessive inflammation promotes end-organ pathology, leading to renal and pulmonary compromise. The spleen is the immunodominant organ in babesiosis. This feature, along with the clearance of parasitized RBCs, explains why asplenia is a major risk factor for severe disease. Protective immunity involves CD4+ T cells, particularly Th1 cells, as revealed by high-grade parasitemia in mice depleted of CD4+ T cells or treated with an interferon γ–neutralizing antibody. The importance of CD4+ T cells is corroborated by the severity of babesiosis in patients

with AIDS and in allograft recipients. In immunocompetent mice, Tfh cell expansion is accompanied with germinal center formation and antibody secretion. Although nearly every immunocompetent patient tests positive for B. microti antibody at diagnosis, a role for antibodies is uncertain. Persistent, relapsing babesiosis often occurs in patients treated with rituximab for a cancer or an autoimmune disorder; this observation suggests that B cells, and presumably antibodies, are criti cal for parasite clearance in some individuals. ■ ■DIAGNOSIS A diagnosis of babesiosis should be considered for patients who experi ence symptoms compatible with babesiosis and may have been exposed to ticks in an endemic area, particularly from late spring to early fall, or were transfused with blood components, particularly packed RBCs, in the past 6 months. Given that I. scapularis ticks can be coinfected with B. microti and B. burgdorferi, babesiosis should be considered in any Lyme disease patient for whom symptoms worsen or do not abate within days or weeks of initiation of appropriate antibiotic therapy. Conversely, because one-half of patients diagnosed with babesiosis are infected with B. burgdorferi, a diagnosis of babesiosis should prompt a diagnostic evaluation for Lyme disease. Other tick-borne pathogens, although rarely implicated in cases of coinfection with B. microti, may be considered; these include Anaplasma phagocytophilum (Chap. 192) and Borrelia miyamotoi (Chap. 190). Routine Laboratory Testing The complete blood count often is remarkable for anemia. An elevated reticulocyte count signifies stress-induced erythropoiesis. Low levels of haptoglobin or elevated levels of lactate dehydrogenase are consistent with hemolysis. Severe anemia often is preceded by severe thrombocytopenia. The white blood cell (WBC) count is reduced, unchanged, or elevated. Elevated levels of alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase signify hepatocyte injury. Elevated total bilirubin levels result from hemolysis but may also denote hepatic compromise. Elevated levels of blood urea nitrogen and serum creatinine indicate renal compromise. Urinalysis may reveal excess urobilinogen, hemo globinuria, and/or proteinuria. Given that babesiosis is an imitator of HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, a diagnosis of babesiosis should be considered for pregnant women who are at risk of tick exposure and have laboratory abnormali ties that define this syndrome. There is no consensus on the use of a particular laboratory param eter as predictor of severe babesiosis. In a study of severe disease as defined above (see “Clinical Manifestations”), a total bilirubin level of >1.9 mg/dL was highly predictive of severe disease, whereas WBC counts of <5 × 103/μL were associated with a better prognosis. Param eters associated with severe disease also included WBC counts of

> 10 × 103/μL and creatinine levels of >1.2 mg/dL. An earlier study identified alkaline phosphatase levels of >125 IU/L and WBC counts of 5 × 103/μL as strong predictors of severe disease, in this case defined as a hospital stay of >2 weeks, an ICU stay of >2 days, or death. Specific Testing A definitive diagnosis of babesiosis is made by microscopic examination of Giemsa-stained thin blood smears

A B C D FIGURE 232-2 Giemsa-stained thin blood films showing Babesia microti parasites. B. microti is an obligate parasite of erythrocytes. Trophozoites may appear as ring forms (A) or as ameboid forms (B). Merozoites can be arranged in tetrads that are pathognomonic (C). Extracellular parasites can be noted (D), particularly when parasitemia is high. (Reproduced with permission from E Vannier, PJ Krause: Human babesiosis. N Engl J Med 366:2397, 2012.) (Fig. 232-2) or

amplification of Babesia DNA in blood. Babesia trophozoites appear round, oval, or ameboid. The ring form is most common and lacks the central brownish (hemozoin) deposit typical of Plasmodium falciparum late-stage trophozoites (see Fig. A2-1). For travelers who have returned from P. falciparum–endemic areas and reside in a Babesia-endemic area, a negative result in the BinaxNOW malaria test readily rules out falciparum malaria when microscopy cannot. The presence of extracellular merozoites, particularly when parasitemia is high, and the absence of gametocytes and schizonts also distinguish babesiosis from malaria. Merozoites are arranged in pairs and occasionally in tetrads (the “Maltese cross”). Tetrads are pathognomonic of babesiosis and can be seen in human erythrocytes infected with B. microti, B. duncani, B. venatorum, or B. divergens–like organisms. Parasitemia typically ranges from 0.1 to 10% in immuno competent patients but has reached 30–40% in immunocompromised patients. Parasitemia of >4% is a risk factor for severe, complicated disease. Splenic complications, however, often occur in patients with low-grade parasitemia (median, 1%; range, 0.1–30%). If parasites cannot be identified by microscopy and babesiosis is still suspected, amplification of Babesia DNA is recommended. Real-time polymerase chain reaction (PCR) assays, which amplify the parasite 18S rRNA gene, detect as few as 1–10 parasites/μL of blood. Use of a fluorescent probe allows for speciation of the causative agent. Realtime PCR is recommended for the monitoring of low-grade infection in patients at risk of relapsing babesiosis. A single positive serologic result is not sufficient to establish a diagnosis of babesiosis because antibodies can persist for >1 year after the illness has resolved and the parasite has been cleared. An indirect fluorescent antibody test is most commonly used. For B. microti, IgM titers of ≥1:20 and IgG titers of ≥1:64 are considered positive. IgG titers of ≥1:1024 suggest active or recent infection. Antibodies to B. microti do not react with B. duncani or B. divergens antigen. Sera from patients infected with B. venatorum or B. crassa–like organisms react with B. divergens antigen.

TREATMENT Babesiosis MILD TO MODERATE B. MICROTI ILLNESS Mild to moderate babesiosis caused by B. microti is treated with atovaquone plus azithromycin administered orally for 7–10 days. Dosages for adults and children are provided in Table 232-1. Symptoms usually abate within 48 h after initiation of therapy and resolve within 1–2 weeks. If symptoms persist despite therapy for babesiosis, initiating doxycycline while testing for B. burgdorferi or other tick-borne pathogens such as A. phagocytophilum and

B. miyamotoi is essential. Fatigue may persist for weeks to months but does not warrant, on its own, that treatment be extended or resumed. Parasite DNA can be detected for as long as 3 months, but follow-up PCR testing is not recommended because relapse of infection in immunocompetent individuals is unlikely. SEVERE B. MICROTI ILLNESS First-Line Antimicrobial Therapy The preferred regimen for the treatment of severe babesiosis caused by B. microti is oral atova quone plus IV azithromycin (Table 232-1). Use of this combina tion is supported by a retrospective study of 40 patients who were admitted for severe babesiosis, including 11 who were admitted to the ICU. All but 1 of the 40 patients improved following ini tiation of treatment with atovaquone plus azithromycin, and were discharged. Clindamycin plus quinine, the first regimen to ever bring cure to a babesiosis patient, is an alternative choice. Use of quinine is impeded by a risk for QTc prolongation and cinchonism, including tinnitus; these adverse events often require premature discontinuation. A prospective, nonblind, randomized clinical trial established that atovaquone plus azithromycin is as effective as clindamycin plus quinine in clearing B. microti parasites and resolving symptoms of non-life-threatening babesiosis. Adverse events were reported

by 15% of patients treated with atovaquone plus azithromycin but 72% of patients treated with clindamycin plus quinine. No trial has compared the 2 regimens for treatment of severe babesiosis. CHAPTER 232 Babesiosis Intravenous azithromycin should be initiated at 500 mg/d, along with atovaquone. Laboratory parameters should be monitored daily until symptoms abate and parasitemia is <4%. Thereafter, azithro mycin can be administered orally. If the patient has an intact spleen and is not immunocompromised, the dosage can be reduced to 250 mg/d. The regimen is administered for 7–10 days, but the duration should be extended if symptoms persist. If the patient is asplenic or immunocompromised, azithromycin should be main tained at 500 mg/d. Given the risk for prolonged or relapsing babe siosis in such patients, the regimen should be administered until symptoms have resolved and parasites are no longer seen on blood smear for at least 2 weeks. Adjunct Exchange Transfusion RBC exchange (RCE) is rec ommended when parasitemia is high and the clinical status of the patient deteriorates in the context of complications such as severe hemolysis or critical organ dysfunction, particularly renal or pulmonary compromise. The primary purpose of RCE is to rapidly reduce parasite burden; RCE also corrects anemia. Plasma exchange seldom is used in severe, complicated babesiosis although it removes circulating inflammatory mediators and byproducts of hemolysis such as free hemoglobin, free heme, and unconjugated bilirubin. Therapeutic apheresis is performed in close consultation with transfusion medicine services. The criteria for RCE are not strictly defined. It is common prac tice to initiate RCE when parasitemia is >10%, although no study has been conducted to identify the threshold above which RCE pro vides greatest benefit. A recent case series illustrates the limitation of using parasitemia as the sole criterion to initiate RCE in the hope of preventing death. In this study of 19 patients, pre-RCE parasit emia (mean, 12.9%; 95% confidence interval [CI], 9.4–16.4) was a predictor of post-RCE length of hospital stay but not of mortality;

TABLE 232-1 Treatment of Human Babesiosis ADULTS CHILDREN Mild to Moderate B. microti Infectiona Atovaquone (750 mg q12h PO) plus Azithromycin (500 mg/d PO on day 1 followed by 250 mg/d PO on subsequent days) Atovaquone (20 mg/kg q12h PO; maximum, 750 mg/dose) plus Azithromycin (10 mg/kg qd PO on day 1 [maximum, 500 mg], 5 mg/kg qd PO thereafter [maximum, 250 mg]) Severe B. microti Infectionb,c Preferredd Preferred Atovaquone (20 mg/kg q12h PO; maximum, 750 mg/dose) plus Azithromycin (10 mg/kg qd IV followed by 10 mg/kg qd PO [maximum, 500 mg]) Alternative Clindamycin (7–10 mg/kg q6–8h IV followed by 7–10 mg/kg q6–8h PO [maximum, 600 mg/dose]) plus Quinine (8 mg/kg q8h PO; maximum, 650 mg/dose) Consider exchange transfusion Atovaquone (750 mg q12h PO) plus Azithromycin (500 mg qd IV followed by 250–500 mg qd PO) Alternativee,f Clindamycin (600 mg q6h IV followed by 600 mg q8h PO) plus Quinine (650 mg q6–8h PO) Consider exchange transfusion B. divergens Infectiong Immediate complete exchange transfusion plus Clindamycin (600 mg q6–8h IV) plus Quinine (650 mg q8h PO) Immediate complete exchange transfusion plus Clindamycin (7–10 mg/kg q6–8h IV; maximum, 600 mg/dose) plus Quinine (8 mg/kg q8h PO; maximum, 650 mg/dose) PART 5 Infectious Diseases aTreat for 7–10 days. bTreat for 7–10 days, but extend duration if symptoms persist. cFor severely immunocompromised patients, antimicrobial therapy should be given for at least 6 consecutive weeks, including 2 final weeks during which parasites are no longer detected on blood smear. dIf the risk of QTc prolongation or allergy associated with use of azithromycin is a concern, clindamycin can be substituted for azithromycin. For severely immunocompromised patients, IV clindamycin can be added to atovaquone plus azithromycin at initiation of treatment. eClindamycin plus quinine is no longer the preferred regimen because quinine often is discontinued due to QTc prolongation or other side effects, including tinnitus. This regimen can be considered for cases that

respond poorly to atovaquone plus azithromycin. fOther alternative regimens have been used successfully, as documented in a limited number of case reports. If quinine toxicity is a concern, atovaquone can be substituted for quinine. For cases that respond poorly to atovaquone plus azithromycin, atovaquone-proguanil can be added to the two-drug regimen or can be substituted for atovaquone. gA few cases of B. divergens infection in Europe have been treated successfully with atovaquone plus azithromycin or atovaquoneproguanil plus azithromycin. this finding is consistent with the concept that end-organ dysfunc tion is a correlate of host inflammation rather than parasite burden. Post-RCE parasitemia (mean, 3.4%; 95% CI, 1.9–4.9) was associated neither with post-RCE length of hospital stay nor with mortality; this finding advocates against the use of repeat RCE. There was a trend toward an association between creatinine levels at admission and mortality, pointing to the greater benefit of RCE in patients with renal compromise. RCE has been withheld when the patient is stable and parasitemia has begun to resolve following initiation of antimicrobial therapy. In a study that compared 9 such patients with 19 patients who underwent RCE and received antimicrobial therapy, the two groups differed neither by the parasitemia at

admission (mean, 11.0% vs 11.6%) nor by the time to parasitemia <1% (day 7 vs day 8). Highly Immunocompromised Patients Patients are at risk for per sistent, relapsing babesiosis when the immune response to Babesia is severely impaired. Major risk factors include asplenia, HIV/ AIDS, and immunosuppressive regimens given for transplantation, an autoimmune disorder, or malignancy. Many of these regimens include rituximab or another B cell–depleting antibody. Antimi crobial therapy should be administered for at least 6 consecutive weeks, including 2 weeks beyond the first definitive negative PCR

test for B. microti. Given the duration of treatment, atovaquone plus azithromycin is the preferred regimen. Azithromycin should be administered intravenously and initiated at 500 mg/d. Laboratory parameters should be monitored daily until symptoms abate and parasitemia is <4%. Thereafter, azithromycin can be administered orally, but the dosage should be maintained at 500 mg/d because lower dosages may promote antimicrobial resistance. Once the patient is no longer critically ill, routine laboratory testing can be performed every 2 to 3 days. When parasites are no longer observed on blood smear, real-time PCR should be used to monitor the infec tion. After discontinuation of therapy, close follow-up is recom mended. If symptoms recur, blood smears and/or real-time PCR should be ordered. Antimicrobial Resistance Parasitologic or clinical relapse has been documented in highly immunocompromised patients, par ticularly when antimicrobial therapy is interrupted or administered at a reduced dosage. Some patients who relapse while or after being treated with atovaquone plus azithromycin have been managed with clindamycin plus quinine (Table 232-1, footnote e). When quinine toxicity is a concern, clindamycin has been added to atovaquone plus azithromycin. An informed approach is to identify mutations that have arisen in the parasite genome and may explain antimicrobial resistance. Atovaquone targets the parasite cytochrome b (Cytb). When resistance to atovaquone is predicted to be partial, atovaquone-proguanil

can be substituted for atovaquone (Table 232-1, footnote f). The rationale is that, as with P. falciparum, proguanil lowers the concentration of atovaquone required to collapse the mitochondrial membrane potential. Resistance to azithromycin has been attrib uted to missense mutations in the ribosomal protein subunit L4 gene (RLP4) and to a mutation in domain V of the 23S rRNA gene, which carries the peptidyl transferase activity of the parasite ribo some. Domain V is also the target of clindamycin. When resistance to azithromycin is explained by a mutation in

RPL4, clindamycin can be substituted for azithromycin. A mutation in domain V that prevents binding of azithromycin and clindamycin precludes sub stitution of one for the other. Such mutation was recently identified in a patient who relapsed while being treated with a three-drug regimen that included azithromycin and clindamycin. Following initiation of tafenoquine at the loading dose of 600 mg (given over 3 consecutive days), parasitemia rapidly declined. Tafenoquine was administered along with atovaquone and proguanil. Maintenance therapy, which consisted of a 300-mg weekly dose of tafenoquine, was discontinued 5 weeks after the last positive B. microti PCR test. Tafenoquine, which acts by inducing reactive oxygen species, is well suited to substitute for drugs that target a particular gene product. Tafenoquine should not be prescribed to patients with glucose6-phosphate dehydrogenase deficiency because their RBCs have reduced antioxidant capacity and would not sustain the oxidative stress caused by tafenoquine. Splenic Rupture Splenic rupture typically occurs in young, healthy patients with low-grade parasitemia. If the patient is hemo dynamically unstable, emergent splenectomy should be performed. If the patient is hemodynamically stable but bleeding persists, splenic arterial embolization should be considered. In the absence of hemoperitoneum, splenic rupture should be managed without surgery but with careful hemodynamic monitoring. Removal of the spleen leaves patients at risk for relapsing babesiosis or severe disease caused by other microorganisms. OTHER BABESIA INFECTIONS B. duncani and B. divergens–like infections typically have been treated with IV clindamycin (600 mg three or four times daily or 1200 mg twice daily) plus oral quinine (600–650 mg three times daily) for 7–10 days. RBC exchange is initiated for patients with severe hemolytic anemia and/or end-organ failure. In a recent case of severe B. divergens-like infection, a RBC exchange was performed and cure was achieved following a 2-week course of atovaquone plus azithromycin.

Revision #1
Created 2026-01-06 16:32:47 UTC by Omar Ayman
Updated 2026-01-06 16:32:47 UTC by Omar Ayman