symptomatic children fail to control an outbreak of diarrhea, consideration can be given to treating all infected children.[231] Treatment-based strategies for transmission prevention in endemic settings, however, have not proven beneficial. Although metronidazole exposure within the previous 7 days decreased the likelihood of *Giardia* detection[60] in separate community-based studies of children in high-transmission endemic settings, community-based administration of metronidazole, albendazole, or nitazoxanide did not diminish *Giardia* prevalence.[118,195,232]

Human milk can be protective against *Giardia*. Both human and animal breast milk can contain anti-*Giardia* antibodies; studies have demonstrated protection of breastfeeding infants from symptomatic infection.[114,233,234]

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The complete reference list is available online at Expert Consult.

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280 *Trichomonas vaginalis*

Jane R. Schwebke and Laura Hinkle Bachmann

SHORT VIEW SUMMARY

Microbiology and Epidemiology
- *Trichomonas vaginalis* is a flagellated parasite.
- Infection is through sexual transmission.
- Susceptibility to human immunodeficiency virus (HIV) infection may be increased in infected women.

Diagnosis
- Infection causes vaginitis in women and may cause urethritis in men; it is often asymptomatic.
- In women, most cases are diagnosed using wet prep microscopy of vaginal fluid as the point-of-care test, but this lacks sensitivity.
- The gold standard for diagnosis is nucleic acid amplification testing.

Therapy
- Metronidazole is the usual therapy.
- Resistance to metronidazole may occur.
- Tinidazole may be more effective.

Prevention
- Sexual partners should be treated.
- Condoms prevent infection.

Trichomonas vaginalis is the causative agent of trichomoniasis, a common cause of vaginitis. In men, it may cause urethritis but is more commonly asymptomatic. Despite being a readily diagnosed and treatable sexually transmitted disease (STD), trichomoniasis is not a reportable infection and its control has received relatively little emphasis from public health STD control programs. More recently, however, recognition of the high rates of disease and of associations of trichomoniasis in women with adverse outcomes of pregnancy and increased risk for human immunodeficiency virus (HIV) infection suggest a need for increased control efforts.

TAXONOMY

Trichomonas vaginalis is a parasitic pear-shaped protozoan, with an average size of 10 × 7 µm (Fig. 280.1). It has four free flagella and one recurrent flagellum, along the outer margin of the undulating membrane; a costa at the base of the undulating membrane; and an axostyle extending through the cell.[1] Unlike most eukaryotes, *T. vaginalis* lacks mitochondria and instead uses the hydrogenosome to accomplish fermentative carbohydrate metabolism, with hydrogen as the electron acceptor. The hydrogenosome appears to have a common ancestry with mitochondria based on similarities in protein import.[2] However, major differences exist between hydrogenosomes and mitochondria in that hydrogenosomes lack cytochromes, mitochondrial respiratory chain enzymes, and their own DNA.

Trichomonas tenax, found in oral gingival and tracheobronchial sites, and *Pentatrichomonas hominis,* isolated from the intestinal tract, are considered nonpathogenic. Each human species has specific tropism for its site of infection. *Tritrichomonas foetus,* which is found exclusively in cattle, is perhaps the nonhuman trichomonad most similar to *T. vaginalis.* Aside from *T. foetus* having three anterior flagella (vs. four in *T. vaginalis*), there are few morphologic differences between the parasites, and *T. foetus* causes the STD known as bovine trichomoniasis. *Tritrichomonas foetus* can be invasive to the fetus, having been demonstrated in the placenta and the fetal lung, gut, and lymph nodes, and is a known cause of abortion in infected cattle.[3]

The life cycle of *T. vaginalis* is simple in that the trophozoite is transmitted through coitus and no cyst form is known. The trophozoite divides by binary fission and, in natural infections, gives rise to a population in the lumen and on the mucosal surfaces of the urogenital tracts of humans. In an infected person there are estimated to be 10^1 to 10^5 protozoa/mL of vaginal fluid.[4] The organisms create microulcerations in the genital mucosa by direct contact, mediated by surface proteins.[5]

Our current understanding of immunity to *T. vaginalis* has come largely from observations of responses in human patients and experimentation using in vitro and animal models of the related species *T. foetus.* Natural infection seems to produce immunity that is only partially protective, because reinfection of patients can be as high as 30% on follow-up.[6] The presence of *T. vaginalis* in the reproductive tract results in parasite-specific antibodies in the reproductive tract and, in most cases, circulating antibodies in the serum[7]; there is also evidence of lymphocyte priming, as detected by antigen-specific proliferation of peripheral blood mononuclear cells.[8] Thus natural infection with *T. vaginalis* results in priming of acquired immune responses. A study of patients infected with *T. vaginalis* and HIV indicated no evidence of increased levels or duration of parasite infection in these patients compared with those in patients infected with *T. vaginalis* but not HIV.[9] These observations may indicate that innate immunity involving chemotaxis and subsequent influx of neutrophils is much more important than acquired immunity in controlling infections with *T. vaginalis,* because neutrophils are often the most numerous leukocytes present in response to infection.[10]

The genome of *T. vaginalis* has been sequenced and provides considerable resources that may be used to define genes important in the pathogenesis of human trichomoniasis. The release of the 5X genome sequence data makes the most comprehensive genomic sequence of this parasite available to date.[11]

EPIDEMIOLOGY

Humans are the only natural host of *T. vaginalis.* Trichomoniasis is an extremely common infection in the United States and worldwide. The prevalence of trichomoniasis in inner-city US STD clinics typically approaches 25% and may be higher in certain populations. In Los Angeles, for example, the prevalence among African-American patients at a public clinic was 38%.[12] Among women ages 14 to 19 years, the overall prevalence of trichomoniasis in the United States was recently found to be 3.1%, but among African Americans the prevalence was 13.3%.[13] An estimate of the incidence of STDs in the United States yielded an annual incidence of trichomoniasis of 7.4 million new cases.[14] The World Health Organization has estimated that this infection accounts for almost 50% of all curable infections worldwide.[15] Studies of African

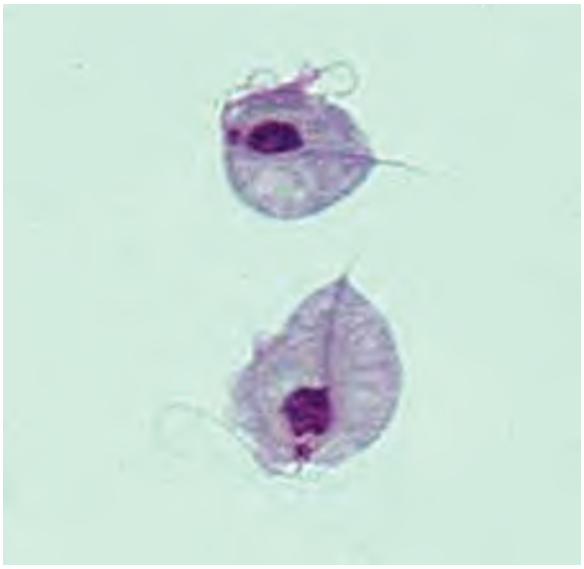

FIG. 280.1 ***Trichomonas vaginalis.*** *(From Centers for Disease Control and Prevention, National Center for Infectious Diseases, Division of Parasitic Diseases.)*

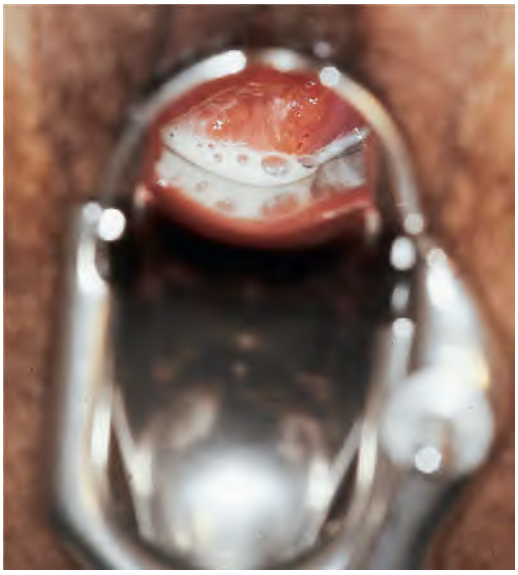

FIG. 280.2 **Vaginal discharge in a patient with trichomoniasis.** Note the bubbles, which give the discharge a "frothy" appearance.

populations have reported the prevalence of vaginal trichomoniasis to be between 11% and 25%. Laga and colleagues reported an incidence of 38% during a 4-month exposure interval among HIV-infected women in Zaire.[16]

Epidemiologically, *T. vaginalis* infections are commonly associated with other STDs and are a marker of high-risk sexual behavior. Trichomoniasis is frequently seen concomitantly with other STDs, particularly gonorrhea. Unlike other STDs, which have a higher prevalence among adolescents and young adults, the rates of trichomoniasis are more evenly distributed among sexually active women of all age groups, probably as a result of a lack of an organized disease control effort for this infection.[17] Although survival on fomites is documented, the organism is thought to be transmitted almost exclusively by sexual activity.[18] Vertical transmission from mother to infant can occur rarely and cause genital infection or respiratory distress.

The reported prevalence of urethral infection with *T. vaginalis* in males has varied, depending on the population studied and the diagnostic techniques used. In a series of sentinel studies using cultures of urine, urethra, coronal sulcus, and semen, Krieger and associates reported a prevalence of 11% in men attending an STD clinic.[19] Urethritis was present in half of the men with *Trichomonas* as the sole urethral pathogen. In a similar study conducted at an STD clinic in Denver, investigators found a prevalence rate of 2.8% by using urine sediment culture.[20] At an STD clinic in Birmingham, Alabama, *T. vaginalis* was detected by polymerase chain reaction assay in 17% of men attending for a new-problem visit or screening. There was no significant difference in the detection of the organism between men with and without urethral symptoms (20% and 14.5%, respectively). Of men with nongonococcal urethritis (NGU), nearly as many had *T. vaginalis* detected as had *Chlamydia* (19.9% and 25.2%, respectively).[21] Detection of *T. vaginalis* in men is increased if semen is tested in addition to urine and urethral specimens.[22]

CLINICAL MANIFESTATIONS

The organisms create microulcerations in the genital mucosa by direct contact, mediated by surface proteins.[5] In women, it is the squamous epithelium of the vagina that is infected. Interestingly, although 2% to 17% of female neonates may have vaginal colonization if the mother is infected, the infection may not be sustained once the maternal effects of estrogen wear off and the vaginal pH becomes neutral.[23] Neonatal respiratory tract infections with *T. vaginalis* have also been reported.[24] Detection of *Trichomonas* infection in older children should raise the suspicion of child abuse.[25]

TABLE 280.1 Sensitivity of Clinical and Laboratory Findings in Vaginal Trichomoniasis

	CLINICAL MANIFESTATION	PERCENT POSITIVE
Symptoms	None	9–56
	Discharge	50–75
	Malodorous	~10
	Irritating, pruritic	23–82
	Dyspareunia	10–50
	Dysuria	30–50
	Lower abdominal discomfort	5–12
Signs	None	~15
	Vulvar erythema	10–20
	Excessive discharge	50–75
	Yellow, green	5–20
	Frothy	10–50
	Vaginal wall inflammation	40–75
	Strawberry cervix (direct visualization)	1–2
	Colpitis macularis (colposcope)	45
Laboratory findings	pH >4.5	66–91
	Positive whiff test	~75
	Excess polymorphonuclear neutrophils on wet mount	~75

Data from Honigberg BM, ed. Trichomonads Parasitic in Humans. *New York: Springer-Verlag; 1990; Bickley LS, Krisher KK, Punsalang A Jr, et al. Comparison of direct fluorescent antibody, acridine orange, wet mount, and culture for detection of Trichomonas vaginalis in women attending a public sexually transmitted disease clinic.* Sex Transm Dis. *1989;16:127–131; and Rein MF. Uncertainties and controversies in trichomoniasis. In: Sobel JD, ed.* Vulvovaginal Infections: Current Concepts in Diagnosis and Therapy. *New York: Academy Professional Information Services; 1990:73–85.*

The incubation period of this infection is unknown; however, human challenge studies done in the 1940s suggested an incubation period of 4 to 28 days in women.[26] The clinical manifestations of trichomoniasis in the female are summarized in Table 280.1. Symptoms in women include vaginal discharge, pruritus, and irritation. Signs of infection include vaginal discharge (42%), odor (50%), and edema or erythema (22% to 37%). The discharge is classically described as frothy, but it is actually frothy in only about 10% of patients (Fig. 280.2). The color of the discharge may vary. Colpitis macularis (strawberry cervix) is a specific clinical sign for this infection but is detected with reliability only by colposcopy and rarely during routine examination.[10] Other complaints may include dysuria and lower abdominal pain; the cause

of the latter is unclear. The urethra is also infected in most women.[27] Almost 50% of all women with *T. vaginalis* are asymptomatic[28]; therefore if these women are not screened, the diagnosis will be missed. The extent of the inflammatory response to the parasite may determine the severity of the symptoms. Factors that influence the host inflammatory response are not well understood but may include hormonal levels, coexisting vaginal flora, and strain and relative concentration of the organisms present in the vagina. In men the infection is usually asymptomatic, but some studies have suggested that it is a more common cause of NGU than was previously recognized[19,21] and should certainly be considered as a diagnostic possibility in a man who does not respond to initial therapy for NGU. Trichomoniasis in men may also rarely cause epididymitis, prostatitis, and superficial penile ulcerations.[29] Spontaneous resolution of trichomoniasis in men has been reported.[30]

DIAGNOSIS

Direct microscopic examination of vaginal fluid for the presence of motile trichomonads is the most common diagnostic method employed for the detection of trichomoniasis. However, even for skilled diagnosticians, the sensitivity of this test varies from 40 to 60%, and may be less in asymptomatic women.[31] Sensitivity decreases dramatically if specimen transport time is longer than 10 minutes.[32] The pH of the vaginal fluid will usually be higher than 4.5 in women with trichomoniasis but can be normal (≤4.5). In the latter cases, the trichomonads are often sparser because they prefer a more alkaline pH. Neutrophils as well as altered vaginal bacterial microbiota are often seen. Trichomoniasis is most often associated with intermediate vaginal microbiota as defined by Nugent criteria, raising the possibility that *T. vaginalis* may in some way be able to alter the vaginal microbiota composition to enhance its survival.[33] Culture media are commercially available and until recently have been the gold standard for diagnosis, but the cultured specimen requires incubation for up to 7 days prior to finalization.[34] Though not recommended routinely, culture is currently the only acceptable specimen type for susceptibility testing. Additional tests include the Affirm VPIII (Becton Dickenson, Franklin Lakes, NJ), a nucleic acid probe hybridization semiautomated system that also detects candidiasis and bacterial vaginosis and has results available in less than an hour. The OSOM Trichomonas Rapid Test (Sekisui, Lexington, MA), an antigen detection test using immunochromatographic capillary flow dipstick technology, is Clinical Laboratories Improvement Amendments–waived with results available in 10 minutes and sensitivity estimates from 77% to 98%, with specificities of 99% to 100%. Finally, AmpliVue Trichomonas assay and Solana Trichomonas assay (Quidel, San Diego, CA) use an isothermal helicase-dependent amplification-based method to detect trichomonas DNA, with results available within an hour and performance characteristics comparable to culture. All of these tests are currently licensed only for vaginal specimens, can be used as point of care tests, and have sensitivities of about 80%.[35,36] They may be a good choice if microscopy is not available.

Nucleic acid amplification tests (NAATs) are now commercially available for the diagnosis of trichomoniasis and have replaced culture as the gold standard diagnostic test. Genital (endocervical, provider and patient-collected vaginal swabs), urine, and liquid PAP-based specimens are acceptable, with some variation depending on the specific NAAT test being utilized.[37] With sensitivities greater than 90% and specificities from 95% to 100%, current US Food and Drug Association (FDA)–approved NAATs include the Aptima *Trichomonas vaginalis* assay (Hologic, San Diego, CA); the ProbeTec *Trichomonas vaginalis* Q^x assay (BD Diagnostics, Franklin Lakes, NJ); and the Xpert TV test (Cepheid, Sunnyvale, CA),[38] which was recently approved by the FDA for use with male urine. Diagnosis in general is much more difficult for males, with the best culture results obtained by combining urethral swabs and urine sediment into one specimen. However, compared with NAATs, this method is highly insensitive for use in men.[39] Although most are not approved for men by the FDA, several studies have found NAATs to be highly sensitive and specific in this population and these tests are available from laboratories that have performed the necessary validation studies.[39]

Lack of suitable screening and diagnostic tests for males has hampered public health control efforts of the disease. The increasing use of NAATs testing in women and men should be of great importance in this regard.

THERAPY

In most cases, the infection is easily treated with a single 2-g oral dose of metronidazole or tinidazole, and because it is an STD, sexual partners should be routinely treated.[40] The reported cure rates are 90% to 100%. Failure to treat the male sexual partner is likely the most common cause of recurrent disease in women and should be explored before assuming that the woman has a strain of *T. vaginalis* that is resistant to metronidazole. Metronidazole intravaginal gel has limited efficacy and should not be used. Although there continues to be some controversy about the safety of metronidazole in pregnancy, there has never been a documented case of fetal malformation attributed to its use, even when it is used in the first trimester.[41] Tinidazole has a plasma half-life twice that of metronidazole (12–14 hours for tinidazole vs. 6–7 hours for metronidazole)[42] and appears to be better tolerated, with fewer gastrointestinal side effects.

Resistance has been reported, estimated to be from 2.5% to 10% for metronidazole and less than 1% for tinidazole.[43] One mechanism of development of anaerobic resistance to metronidazole is controlled by hydrogenosomes, in that metronidazole competes for hydrogen as an electron acceptor. In metronidazole-resistant *T. vaginalis,* the expression levels of the hydrogenosomal enzymes pyruvate ferredoxin oxidoreductase, ferredoxin, malic enzyme, and hydrogenase are reduced dramatically, which probably eliminates the ability of the parasite to activate metronidazole.[44] Resistance has also been associated with mutations in nitroreductase genes.[45] Resistance is relative and can usually be overcome with higher doses of oral metronidazole. However, there does not appear to be a definitive correlation between in vitro and in vivo resistance. Intravenous formulations offer no advantage over the oral drug. Some authorities have recommended higher doses of oral medication in combination with pharmacy-prepared intravaginal preparations.

Tinidazole, with its more favorable pharmacokinetics, may be the drug of choice when resistance is encountered. The Centers for Disease Control and Prevention (CDC) tested 195 metronidazole-resistant *T. vaginalis* clinical isolates submitted for minimal lethal concentration (MLC) testing for both metronidazole and tinidazole. The mean aerobic metronidazole MLC was 400 μg/mL compared with an aerobic tinidazole MLC of 100 μg/mL.[46] Several clinical studies have evaluated various doses of tinidazole for treatment of metronidazole-resistant trichomoniasis. The largest series of patients was reported by Sobel and associates.[47] In this study, 20 patients with clinically refractory trichomoniasis (failure to respond to therapy with oral metronidazole, at least 500 mg twice daily for 7 days) were treated with high doses of oral and vaginal tinidazole (2–3 g PO, plus 1–1.5 g intravaginally for 14 days). The cure rate was 92% (22 of 24 patients); no patients discontinued therapy because of side effects. Current CDC recommendations for patients failing a single 2-g dose of metronidazole are to treat next with metronidazole, 500 mg PO twice daily for 7 days, or a 2-g dose of tinidazole immediately. Failing that, treatment with tinidazole or metronidazole at 2 g PO for 5 days is suggested.[40]

There are limited anecdotal reports of success with paromomycin cream; however, this therapy may also be associated with a high incidence of local side effects.[48] A case report of two women with resistant trichomoniasis reported cure with a combination of intravaginal paromomycin cream and high-dose oral tinidazole.[49] There is also a report of cure with prolonged intravaginal boric acid suppositories.[50] Women with asymptomatic infection should be treated. If their infection is left untreated, they may later become symptomatic and may continue to transmit the infection while untreated. Occasionally, patients manifest a true allergy to metronidazole. Because there is no effective alternative, desensitization is the only option.[51]

COMPLICATIONS

Long considered a minor STD, with few associated complications, infection with *T. vaginalis* has more recently been implicated as a cause of preterm delivery in several studies. In a large multicenter study, after adjusting for demographic, behavioral, and microbiologic variables, *T. vaginalis* was significantly associated with low birth weight, premature rupture of membranes, and preterm delivery (relative risk, 1.4).[52] Minkoff and coworkers[53] also documented a significant correlation between trichomoniasis and premature rupture of membranes. In that study,

the incidence of this complication at term was 27.5% in women with *T. vaginalis* infection versus 12.8% in those without ($P = .03$).

Prospective studies of treatment of trichomoniasis during pregnancy for the prevention of preterm birth have yielded disappointing results. Among women with asymptomatic infection treated with metronidazole during the second and third trimesters of pregnancy, a trend toward increased preterm delivery was seen compared with the placebo group. However, the dose of metronidazole used was four times the recommended dose. In addition, the study was stopped prematurely because of a slow accrual of subjects and the trend for increased risk for preterm delivery in the treatment group.[54] A second study, conducted in Uganda, also found that treatment of trichomoniasis during pregnancy resulted in an increase in the incidence of preterm birth. However, this study was actually a subgroup analysis of a larger trial and was not properly designed to determine the effect of treatment of *T. vaginalis* during pregnancy on preterm birth[55]; therefore the question remains unanswered. Since the publication of these reports, the CDC has not revised recommendations for treatment during pregnancy. Trichomoniasis has also been associated with vaginal cuff cellulitis after abdominal hysterectomy.[56]

Acquisition of HIV has been associated with trichomoniasis in several African studies, possibly as a result of the local inflammation often caused by the parasite. Leroy and colleagues[57] found a significant difference between the prevalence of trichomoniasis in a cohort of HIV-infected and uninfected pregnant women in Rwanda (20.2% and 10.9%, respectively; $P = 0.0007$). In a prospective study by Laga and associates,[16] trichomoniasis positivity was significantly associated with HIV seroconversion (odds ratio, 1.9) in a multivariate analysis of a cohort of women in Zaire. Similar findings were reported from a cohort of women in Kenya.[58] The associations between HIV and trichomoniasis, as well as other STDs, may relate to the following: (1) increased shedding of HIV as a result of the local inflammation produced by the STD; (2) increased susceptibility to HIV as a result of the macroscopic or microscopic breaks in mucosal barriers caused by the STD; (3) a higher prevalence of STDs among HIV-infected individuals as a result of common risk factors for both infections; and (4) an increased susceptibility to STDs as a result of the immunosuppression associated with HIV infection. Given the higher prevalence and incidence of trichomoniasis than most other treatable STDs in most studies to date, the attributable fraction of HIV acquisitions caused by trichomoniasis may eclipse the relative contribution of other STDs.[12] The RNA concentration of HIV in the seminal fluid of men with urethritis was significantly higher in men with trichomoniasis than in those with symptomatic urethritis with an unidentified cause.[59] In addition, successful treatment of trichomonal urethritis reduced the levels of HIV RNA so that they were similar to those seen in uninfected control subjects.[60]

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The complete reference list is available online at Expert Consult.

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281 *Babesia* Species

Edouard Vannier and Jeffrey A. Gelfand

SHORT VIEW SUMMARY

Definition

- Babesiosis is an emerging infectious disease caused by hemoprotozoan parasites of the genus *Babesia*.

Epidemiology and Microbiology

- Most cases of human babesiosis occur in the United States, particularly the Northeast and the upper Midwest, and are caused by *Babesia microti*. *B. microti* is primarily transmitted during the bite of an *Ixodes scapularis* nymphal tick but also by transfusion of contaminated blood products, predominantly packed red blood cells. *B. microti* has been the pathogen most frequently implicated by investigations of transfused-related illnesses in the United States and accounted for one-fourth of transfusion-related deaths caused by microbial infection from fiscal year 2010 to fiscal year 2016 (see Chapter 304).
- Human babesiosis also occurs in Europe and East Asia, where the major etiologic agents are *Babesia divergens* and *Babesia venatorum*, respectively.
- Risk factors for severe babesiosis include anatomic or functional asplenia, low $CD4^+$ T-cell counts associated with human immunodeficiency virus/acquired immunodeficiency syndrome or therapy for transplantation, and impaired antibody production associated with chronic immunosuppressive therapy.

Diagnosis

- Fever is the salient symptom, and often is accompanied by chills, sweats, headache, anorexia, and/or myalgia.
- Anemia is the major laboratory finding. Severe anemia often is preceded by severe thrombocytopenia. Elevated levels of lactate dehydrogenase and total bilirubin are consistent with hemolytic anemia.
- The definitive diagnosis is made on Giemsa-stained thin blood smears. Trophozoites often appear as rings. Tetrads of merozoites are pathognomonic.
- If parasites are not visualized on smear but babesiosis remains suspected, polymerase chain reaction assay–based amplification of parasite DNA should be performed.

Therapy (See Table 281.1)

- Mild *B. microti* illness should be treated with a single 7- to 10-day course of oral atovaquone (750 mg every 12 hours) *plus* oral azithromycin (500 mg on day 1, then 250 mg from day 2 onward). Symptoms typically abate within 48 hours and resolve within 2 weeks.
- Severe *B. microti* illness requires hospital admission, and can be complicated by pulmonary edema and respiratory distress. Other complications include congestive heart failure, renal failure, disseminated intravascular coagulation, shock, and splenic rupture. Initial therapy should consist of a 7- to 10-day course of oral atovaquone (750 mg every 12 hours) *plus* intravenous azithromycin (500 mg daily). If symptoms do not abate, therapy should be extended as needed. If microbial resistance is suspected, intravenous clindamycin (600 mg every 6 hours) *plus* oral quinine (650 mg every 8 hours) or oral atovaquone is an alternative.
- If the patient is severely immunocompromised, antimicrobial therapy should be administered for at least 6 consecutive weeks, including 2 final weeks during which parasites are no longer detected on blood smear.
- Partial or complete red blood cell exchange transfusion is recommended for cases with high-grade parasitemia (≥10%), severe anemia (hemoglobin <10 g/dL) in the context of parasitemia, or organ (pulmonary or renal) compromise.

Prevention

- No vaccine is available. Individuals at risk of severe babesiosis should avoid tick exposure in endemic areas. Protective measures include covering exposed skin, applying an acaracide to skin, using permethrin-impregnated clothes, and thoroughly examining the skin for ticks.

The first recorded mention of babesiosis is believed to date to biblical times. In the Book of Exodus, the fifth plague is described as "very grievous murrain" that fell "upon thy cattle which is in the field, upon the horses, upon the asses, upon the camels, upon the oxen and upon the sheep." Bovine babesiosis is still referred to as murrain in the Irish countryside. In 1888, the microbiologist and pathologist Victor Babes attributed the febrile hemoglobinuria and death of cattle in Romania to an intraerythrocytic microorganism.[1] Soon after, Theobald Smith and Frederick Kilborne described a similar piroplasm (*L. pirum*, "pear") in the erythrocytes of Texas cattle with fever. Initially named *Pyrosoma*, this organism became known as *Babesia bigemina*. Smith and Kilborne also identified the tick *Rhipicephalus annulatus* as its vector, establishing for the first time that hematophagous arthropods can transmit an infectious agent to a vertebrate host. The first well-documented case of human babesiosis was reported in 1957 in a 33-year-old splenectomized herdsman who had been grazing cattle on tick-infested pastures near Zagreb, Croatia. The infection was fulminant and fatal. Originally identified as *Babesia bovis*, the causative agent was later reported to be *Babesia divergens*, a parasite of cattle. In 1969, a 59-year-old woman who had summered on Nantucket Island off the coast of Massachusetts presented with a history of fever, headache, and crampy abdominal pain. This patient had an intact spleen, and the causative agent was *Babesia microti*, a parasite of white-footed mice. Andrew Spielman and colleagues identified the vector as the deer tick *Ixodes dammini* (now recognized as *Ixodes scapularis*). As the number of cases on the island grew, the disease became known as "Nantucket fever." Babesiosis caused by *B. microti* is now recognized as endemic on the mainland of the United States, particularly in the Northeast and the upper Midwest.

EPIDEMIOLOGY

United States: *Babesia microti*

Geographic Distribution

Human babesiosis became a nationally notifiable disease in January 2011.[2] Notification is made via the National Notifiable Diseases Surveillance System using the standard case definition developed by the Centers for Disease Control and Prevention (CDC) and the Council of State and Territorial Epidemiologists. In 2014, babesiosis was reportable from 31 states, of which 22 notified the CDC of at least one case.[3] Most cases (>90%) are reported from the seven states with well-established foci of zoonotic transmission (Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, Wisconsin). In the Northeast, areas of high endemicity include islands off the southern coast of New England.[4] On the mainland, babesiosis is highly endemic in southeastern Massachusetts, including Cape Cod, the coastal counties of western

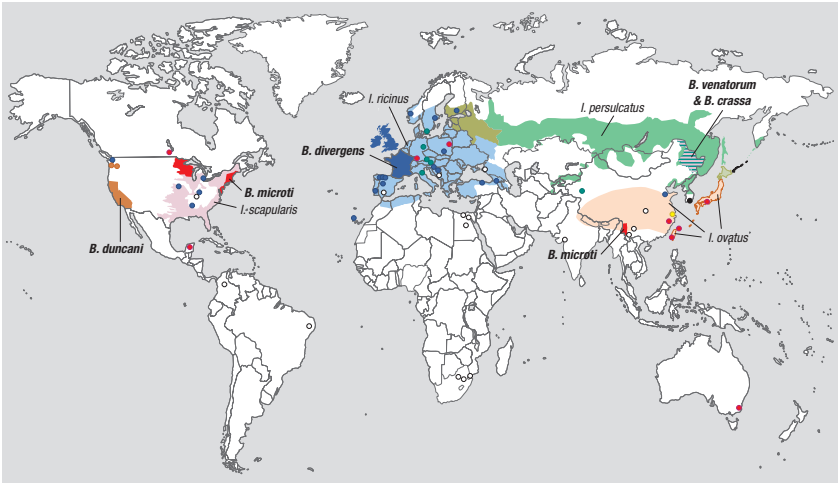

FIG. 281.1 Geographic distribution of human babesiosis and its tick vectors. Dark colors indicate states or provinces where human babesiosis is endemic or sporadic (defined by ≥5 cases), whereas light colors indicate areas where tick vectors are present but human babesiosis is rare (<5 cases), undocumented, or absent. Circles depict single cases, except in three locations (Mexico, Montenegro, and eastern Poland) where all patients were diagnosed at the same hospital. Colors distinguish the etiologic agents: red for *Babesia microti,* orange for *Babesia duncani,* blue for *Babesia divergens,* green for *Babesia venatorum,* pink for *Babesia crassa,* black for KO1, and yellow for *Babesia* sp. XXB/HangZhou. White circles depict cases caused by *Babesia* isolates that were not characterized at the molecular level. Asymptomatic infections and cases of travel-associated babesiosis are omitted. *Ixodes ricinus* and *Ixodes persulcatus* are sympatric in southern Finland, Estonia, Latvia, and northwestern Russia. The island of Hokkaido in northern Japan is enzootic for both *I. persulcatus* and *Ixodes ovatus. (From Vannier E, Krause X. In: Ryan ET, Hill DR, Solomon T, et al, eds.* Hunter's Tropical Medicine and Emerging Infectious Diseases*. 10th ed. Oxford, UK: Elsevier; 2019.)*

Rhode Island and eastern Connecticut, the counties east of the Hudson River in the Lower Hudson Valley (New York), and the south central counties of New Jersey. In the upper Midwest, babesiosis caused by *B. microti* is moderately endemic in Minnesota and Wisconsin (Fig. 281.1).

Incidence and Prevalence

The incidence of babesiosis has steadily increased over the past 30 years. In New York State, the first state to mandate the reporting of babesiosis, more than 5800 cases have been notified to the health authorities. About 1100 cases were reported from 1986 to 2005, and more than 3500 cases in the following decade. The sharp increase noted between 2006 and 2015 resulted from the emergence of babesiosis in the Lower Hudson Valley combined with the maintenance of highly endemic foci on eastern Long Island.[5,6] Along the northeastern seaboard, babesiosis has emerged in areas that were once at the periphery of the "historical heartland," namely southern Maine and southern New Hampshire to the north and Pennsylvania, Delaware, and Maryland to the south.[3,4] In the upper Midwest, the number of annual cases has risen steadily since 2005.[7] A few cases have been reported in Illinois, Indiana, and Michigan.[3] Babesiosis caused by *B. microti* remains an emerging infectious disease in the United States.[1,3,4]

The seroprevalence of antibodies against *B. microti* antigen varies by year, study site, and sample population but has consistently been high in endemic areas, such as Nantucket (7% among blood donors),[8] Block Island (9% among residents),[9] southern Connecticut (0.5%–9% among blood donors),[9,10] Shelter Island (4% in blood donors; 4%–7% among residents),[11] and eastern Long Island (16% among residents).[12] In Minnesota, seroprevalence among blood donors has been reported at 2%.[13] Given that seroprevalence is much higher than prevalence of clinical babesiosis, asymptomatic infection is more common than recognized or reported.

Modes of Transmission

Tick Bite

B. microti is primarily acquired during the blood meal of the tick *I. scapularis,*[14] but only one-half of patients recall a tick bite in the 8 weeks prior to symptom onset.[3] The nymphal stage, the primary vector, is most active from late spring to early summer (see "Microbiology" later).[14] Because the latency period typically lasts from 1 to 4 weeks, one-fifth of cases are diagnosed in June, one-half in July, and another one-fifth in August.[3] Some cases present as early as late spring. Patients who present in late summer or early fall likely acquired the infection from an adult female tick.

Blood Transfusion

B. microti can be transmitted via transfusion of blood components prepared from contaminated blood donated by asymptomatic carriers or symptomatic individuals who did not suspect the infection.[15] Implicated blood donors typically have engaged in outdoor activities.[16] Less than one-fifth have experienced fatigue or fever within 24 months prior to index donation.[16] Even fewer (8%) have experienced chills. Consistent with the seasonality of tick-borne babesiosis, three-fourths of transfusion-transmitted babesiosis (TTB) cases are diagnosed from June through November, with one-fifth in August alone.[17] Given that asymptomatic infection can persist in untreated individuals for longer than a year,[16,18] TTB is diagnosed year-round.[17] Most TTB cases (87%) occur in residents of highly endemic states (see earlier list).[17] Outside endemic areas, TTB typically involves contaminated blood products that are imported from endemic areas or are derived from blood donations by individuals following their return from endemic areas.

More than 250 TTB cases caused by *B. microti* have been identified since the first case was reported in 1979; three-fourths have occurred since 2005.[16,17,19] Most cases involve red blood cell (RBC) units. A few have been attributed to whole-blood–derived platelets contaminated with residual RBCs. At time of transfusion, the age of liquid-stored RBC units has ranged from 4 to 42 days; one platelet unit was 5 days old.[16,17,20] In March 2018, when the US Food and Drug Administration (FDA) approved two tests for donor blood screening (see next paragraph), *B. microti* was still the pathogen most frequently implicated by investigations of transfusion-related illnesses.[19] From fiscal year 2010 to fiscal year 2016, *B. microti* accounted for one-fourth of transfusion-related deaths caused by microbial infection.[21]

Using an arrayed fluorescence immunoassay for detection of *B. microti* immunoglobulin G (IgG) and a real-time polymerase chain reaction (PCR) for detection of *B. microti* DNA, the risk posed by blood donations in some highly endemic areas (Massachusetts and Connecticut) has been carefully assessed.[16] Among donations collected from June 2012 through September 2014, 0.3% reacted in one test or both. Three-quarters of the donations were positive for *B. microti* IgG but negative for *B. microti* DNA, whereas one-fifth were positive for both. Antibody-positive donations were obtained throughout the year. Consistent with the seasonality of tick-borne babesiosis, donations that were DNA positive but IgG

negative were obtained from June through September. Among donors who tested positive for *B. microti* DNA at time of index donation, most (86%) were no longer infected a year later. The median time to parasite DNA clearance was 4.7 months. Among those who tested positive for *B. microti* IgG, only 8% had seroreverted a year later. The median time to seroreversion was 17.1 months. None of the 75,000+ donations screened with the two FDA-approved tests were implicated in a TTB case. In contrast, 1 in 18,000 unscreened donations obtained from the same area was implicated in a TTB case. When five highly endemic states (Connecticut, Massachusetts, Minnesota, New Jersey, New York) were analyzed along with two states that recently emerged as endemic (Maine and New Hampshire), the risk for TTB was estimated at 1 case per 100,000 donations for the period from January 1, 2010 to August 31, 2016.

Transplacental Passage

Unequivocal evidence of transplacental transmission came from a case reported in 2012.[22] A splenectomized mother was admitted after a 10-day history of fever and rigors. Intraerythrocytic *B. microti* ring forms were identified on a blood smear and in the amniotic fluid. On the second day of hospitalization, the mother underwent cesarean section. Immediately after delivery, blood was obtained from the neonate and intraerythrocytic parasites were noted on a thin blood film.

Probable congenital babesiosis has been reported for at least nine other cases.[23–26] For seven cases, mothers were asymptomatic throughout pregnancy. In one such case, *B. microti* likely was acquired during the first trimester of pregnancy.[25] Two symptomatic mothers received a diagnosis of Lyme disease during the last trimester of pregnancy, but *B. microti* infection was not suspected.[24] Symptoms of babesiosis developed in the neonates during the third to the sixth week of life and often consisted of fever accompanied by pallor.[24] Laboratory tests revealed hemolytic anemia, thrombocytopenia, and neutropenia. In all cases but one, anemia was so severe that a blood transfusion was required. At diagnosis, parasitemia ranged from 2% to 40%. When tested for *B. microti* antibody, neonates and their mothers were seropositive. One neonate who presented with tachycardia and respiratory distress required an exchange transfusion, which was performed manually.[26] This neonate had a twin who was seropositive for *B. microti* but remained healthy. In another case, *B. microti* antibody was detected in a heel stick blood sample obtained on the third day of life, raising the possibility that maternal IgG directed against *B. microti* protects newborns from congenital babesiosis very early in life.[23] In addition to vertical transmission, babesiosis has been diagnosed in neonates following blood transfusion.

Solid Organ Transplantation

Two cases of transplantation-associated babesiosis have been described.[27] Both men had received a kidney allograft obtained from the same deceased donor and began experiencing symptoms 5 weeks posttransplantation. The diagnosis of babesiosis was made 8 weeks posttransplantation. Despite immunosuppressive therapy, both men tested seropositive for *B. microti.* Pretransplantation serum samples did not react with *B. microti* antigen, an observation consistent with the denial by these allograft recipients of tick exposure and blood transfusion prior to transplantation. The organ donor, however, had received multiple blood transfusions, including one from a blood donor who tested positive for *B. microti* antibody during the retrospective investigation. It is presumed that some *B. microti* parasites from the blood donor had remained in the vasculature/fluids of the renal allografts at time of transplantation. In support of this explanation, corneas from the deceased organ donor were transplanted but neither recipient presented clinical or serologic evidence of *B. microti* infection.

Risk Factors

Babesiosis caused by *B. microti* often is severe in individuals with one or several of the following risk factors: asplenia,[28–30] X-linked agammaglobulinemia,[29] malignancy,[31] low $CD4^+$ T-cell counts associated with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS),[32,33] blockade of tumor necrosis factor-α (TNF-α) for chronic inflammatory disorders such as inflammatory bowel disease,[34] and immunosuppressive therapy for transplantation,[35,36] B-cell lymphoma, or an autoimmune disorder.[29,32] These risk factors also pertain to the transmission of *B. microti* by blood transfusion. In this setting, given that most cases have significant comorbidity, risk factors for TTB include conditions that require blood transfusion, such as hematologic disorders, cardiovascular surgery or procedure, gastrointestinal disease, bleeding and surgery, and anemia of prematurity.[17] Two-thirds of TTB patients are older than age 50 years, but two-thirds of those younger than age 40 years have a hereditary RBC disorder.[17]

United States: Other *Babesia* Species

Babesia duncani and *B. duncani*–type organisms are the etiologic agents of human babesiosis along the Pacific Coast.[1] The index case (WA1) occurred in a 41-year-old normosplenic man from a forested area of south central Washington State.[37] The four cases in California (CA1–CA4) developed in splenectomized men in their 20s to 40s who lived or had outdoor exposure in areas ranging from Sonoma County to San Bernardino County.[38] The first case of TTB caused by *B. duncani* involved a 76-year-old normosplenic man who had received RBCs donated by a 34-year-old Washington State resident.[39] The second case was diagnosed in a premature male infant who had received two blood transfusions.[40] The implicated donor lived in the San Francisco Bay area and had vacationed in a rural area of central Oregon 3 months prior to donating. The third case involved a 59-year-old patient who had sickle cell disease.[41] The 67-year-old donor reported a possible tick bite during a hike in the San Francisco Bay area. The winter tick *Dermacentor albipictus* presumably is the vector for transmission of *B. duncani*.[41a] The prevalence of *B. duncani* infection remains unclear because clinical cases have been too few to validate the serologic test.

B. divergens–like organisms have caused disease in Arkansas, Kentucky, Michigan, Missouri, and Washington State.[42–45] All six patients were older than 50 years of age, and asplenic. In one case, transfusion is the suspected mode of transmission.[43] The patient lived in Arkansas but blood donated in Missouri was the likely culprit, thereby bringing to three the number of *B. divergens*–like infections that originated in Missouri. Isolates from the five cases that originated in the Midwest were identical to piroplasms found in eastern cottontail rabbits, implying that *Ixodes dentatus* may be a vector for zoonotic transmission of *B. divergens*–like organisms. In Tennessee, three cases were uncovered by querying claims data from a managed care organization.[46] One such case may have been caused by a *B. divergens*–like organism.

Europe: *Babesia divergens*

Approximately 40 cases of babesiosis have been attributed to *B. divergens,* a parasite of cattle that is transmitted by *Ixodes ricinus*.[47] Most cases occurred in France and Ireland, particularly in regions with extensive cattle farming. Isolated cases have been reported from Portugal, Spain, Norway, Sweden, Finland, Georgia (ex-USSR), Turkey, and Croatia (including the index case). Nearly all patients experienced a severe illness and had been splenectomized,[47] although one had a rudimentary spleen and another had functional hyposplenism caused by celiac disease.[48,49] TTB caused by *B. divergens* has not been reported from Europe, although asymptomatic *B. divergens* infection is not uncommon, as indicated by seroprevalence in Slovenia (4.1% of forestry workers), western Austria (2.1% of blood donors), midwestern Germany (4.2% of individuals with clinical or serologic evidence of Lyme borreliosis), and southern Sweden (7.0% of individuals seropositive for *Borrelia burgdorferi* s.l.).[50–51a]

Europe: Other *Babesia* Species

Cases of *B. venatorum* infection have been reported in Italy, Austria, Germany, and Sweden.[52–54] The five patients were splenectomized men older than 50 years of age. Roe deer are a reservoir host for *B. venatorum* in Europe, and the bite of an *I. ricinus* tick is the suspected mode of transmission. The prevalence of asymptomatic infection remains unknown because *B. venatorum* sera cross-react with *B. divergens* antigen. Attributed to *B. divergens* based on morphology and seroreactivity, some early cases of babesiosis in Europe may have been caused by *B. venatorum.*

The first case of *B. microti* infection native to Europe was reported in 2007 from Germany.[55] A 42-year-old woman presented with fever and chest pain 1 week after chemotherapy for acute myeloid leukemia. Intraerythrocytic parasites were observed on Giemsa-stained blood smears and identified as US-type *B. microti.* The platelet concentrate transfused 6 days before the diagnosis of babesiosis had been prepared

from blood donated by an individual who subsequently tested seropositive for *B. microti.* Additional cases were reported in 2016 from northeastern Poland.[56] All six patients were immunocompetent and had been bitten by a tick within 8 weeks prior to presentation. No parasites were seen on blood smear, but a fragment of the *B. microti* 18S ribosomal RNA (rRNA) gene was amplified and sequenced, establishing for the first time that *B. microti* organisms of the Munich lineage can cause disease in humans. Cases of travel-associated babesiosis have been reported throughout Europe and explained by a recent stay in the northeastern United States.[47] Asymptomatic *B. microti* infection is prevalent in residents of rural, forested areas across Europe as indicated by serosurveys conducted in northeastern Poland (4.4% of foresters), eastern Switzerland (1.3% of blood donors), midwestern Germany (8.3% of individuals with clinical or serologic evidence of Lyme borreliosis), eastern France (2.% of foresters who are seropositive for other tick-borne pathogens), and Belgium (9% of patients presenting within 1 month after a tick bite).[50,57–60]

Asia: *Babesia venatorum*

The first case of *B. venatorum* infection in Asia was documented in northwestern China.[61] A series of 48 cases was subsequently reported from northeastern China.[62] All 48 cases reported a tick bite within 2 months prior to seeking medical care; none had received a blood transfusion within 2 years. All had a spleen, but only one-third were older than 50 years. A survey of ticks revealed that the taiga tick *Ixodes persulcatus* is the likely vector for *B. venatorum* in northeastern China.

Asia: Other *Babesia* Species

The first two cases of *B. microti* infection in Asia were documented in Taiwan.[63] A case of TTB was subsequently reported from Kobe, Japan.[64] The isolate has defined the Kobe lineage, one of the four lineages within the *B. microti* species complex.[65] The asymptomatic blood donor resided on the nearby Awaji Island, where the field mouse *Apodemus speciosus* was identified as a reservoir host for Kobe-type organisms.[66] The vector is unknown. *B. microti* organisms of the Hobetsu lineage are found in *A. speciosus* mice throughout Japan, and can be transmitted by *Ixodes ovatus* ticks.[67] Hobetsu-type organisms have infected humans, as revealed by a serosurvey, but no cases of babesiosis have been reported. In mainland China, *B. microti* has caused disease in the southern provinces, particularly in Yunnan along the border with Myanmar.[68,69] At least two cases were caused by US-type organisms. One case was coinfected with *Plasmodium falciparum* and another with *Plasmodium vivax.*[68]

In South Korea, a 75-year-old splenectomized woman who presented with fever and severe anemia was infected with a large *Babesia* species (KO1) that is closely related to organisms found in sheep. A series of 31 cases caused by *Babesia crassa,* a species found in sheep, has been documented in northeastern China.[70] All cases were mild to moderate; none were asplenic.

Rest of the World

A case of US-type *B. microti* has been documented in Australia.[1] On the American continent, a case of *B. microti* infection was identified in Manitoba, Canada, whereas three cases were diagnosed on the Yucatan peninsula, Mexico. Asymptomatic *B. microti* infection has been documented in Bolivia and Brazil. Cases caused by *Babesia* spp. that infect cattle (*B. bigemina*, *B. bovis*) have been reported from Colombia. Asymptomatic infections with these two *Babesia* spp. have been reported from Brazil, Colombia, and Cuba. On the African continent, three cases have been reported from Egypt, of which one was acquired from a pet dog. A case of *B. divergens*–like infection was diagnosed in a splenectomized resident of the Canary Islands. In South Africa, babesiosis was diagnosed in two patients upon their return from Namibia and Zimbabwe. Isolated cases of *B. bovis* infection, of which two were fatal, have been documented in Mozambique.

MICROBIOLOGY

Babesia spp. are protozoa parasites of the phylum Apicomplexa, class Aconoidasida, and order Piroplasmida. More than 100 *Babesia* spp. are known to infect vertebrates, including mammals and birds. In the northern hemisphere, most *Babesia* spp. are maintained in their enzootic cycle by hard-bodied ticks of the genus *Ixodes.* In the United States, *B. microti* is maintained by *I. scapularis* ticks.

The Enzootic Cycle of *Babesia microti*

Ticks and Reservoir Hosts

The life cycle of *I. scapularis* has three active stages (larva, nymph, adult) and requires 2 years for completion.[1,14] In the fall, adult ticks feed primarily on white-tailed deer (*Odocoileus virginianus*). Deer are incompetent hosts for *B. microti* but are essential for the mating of *I. scapularis* and therefore its maintenance in the life cycle. Adult female ticks overwinter in an engorged state and lay eggs in the spring. Because *B. microti* does not reach the ovaries of adult ticks, eggs are free of *B. microti* (no transovarial transmission). Larvae hatch in late July and become infected as they feed in late summer on a wide range of small mammals. The primary reservoir host for *B. microti* is the white-footed mouse (*Peromyscus leucopus*).[14] Other competent reservoirs include short-tailed shrews, eastern chipmunks, and raccoons.[71] Passerines, raptorial birds, and ground-dwelling birds (e.g., wood thrush, veery) are reservoirs but of lesser competence. Fed to repletion, larvae overwinter and molt into nymphs in late spring. If the larva is infected, so can be the nymph (transstadial transmission). Nymphs feed on *P. leucopus* and other vertebrates from May through July. Feeding of nymphs in early summer ensures that *P. leucopus* mice are reservoirs of *B. microti* when larvae feed in late summer. In the fall, nymphs molt into adults.

Parasite Acquisition by Ticks

Soon after attachment of a larva or a nymph, host erythrocytes accumulate in its gut.[1,14] *Babesia microti* pregametocytes mature into gametocytes. Microtubules accumulate at the anterior end of the parasite to form a raylike structure that contributes to the fusion of gametocytes into a zygote. Using an arrowhead structure, zygotes penetrate the tick gut epithelium. The arrowhead structure dissociates, and zygotes translocate to the basal lamina. In the hemolymph, zygotes become ookinetes that travel to the salivary acini. There, ookinetes hypertrophy into sporoblasts, which remain dormant while the larva or nymph overwinters and, until the next tick stage, feeds on a reservoir host or, incidentally, on a human.

Parasite Transmission to Hosts

Larvae, nymphs, and adult ticks all feed on humans, but the nymph is the primary vector for *B. microti* transmission.[1,14] The size of the nymph (<2.5 mm; as small as a poppy seed), its gray ground color, and the inconspicuous feeding site explain why only one-half of patients recall a tick bite.[3] As nymphs attach to the host, their temperatures rise. Sporogony is initiated, and the sporoblast membrane folds. Micronemes and rhoptries appear. The cytoplasm starts to bud from the parent sporoblast, and nuclear division ensues. During the final hours of feeding, which typically last 72 hours, as many as 100,000 sporozoites are deposited in the dermis of the host. Events that lead sporozoites toward the bloodstream are not well understood. *Babesia* sporozoites do not undergo merogony in an exoerythrocytic compartment but readily invade erythrocytes. Surface antigens, particularly glycosylphosphatidylinositol-anchored proteins encoded by genes of the *bmn* family, are thought to mediate initial attachment.[72,73] Micronemes also contribute to host cell invasion, as evidenced by the role of the apical membrane antigen 1 (AMA1),[74] a micronemal protein that anchors in the plasma membrane of the parasite at its apex. A role for AMA1 is consistent with a role for the rhoptry neck protein (RON) macromolecular complex that is projected onto the erythrocyte and anchors in its plasma membrane.[75] As with *Plasmodium* species, the erythrocyte membrane is thought to invaginate as the parasite glides using the moving junction formed by nascent AMA1-RON2 interactions. Once the invasion process is completed, the parasitophorous vacuole gradually disintegrates. The organism differentiates into a trophozoite that moves freely in the RBC cytoplasm and eventually undergoes binary fission, resulting in two to four merozoites (Fig. 281.2). Merozoites egress the erythrocyte, thereby triggering its lysis, and soon invade other erythrocytes.

Classification of *Babesia* Species

Single-Gene Analysis

Using full-length 18S rRNA gene sequences, phylogenetic analysis of the order Piroplasmida has revealed five clades.[76] The first clade contains the *B. microti* species complex as well as *Babesia rodhaini,* a parasite of rodents. The second clade consists of piroplasms found in the western United States and may constitute a species complex because *B. duncani*

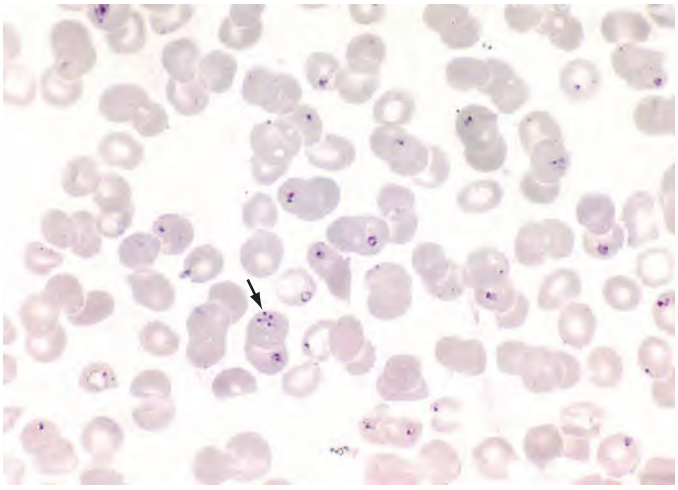

FIG. 281.2 Giemsa stain of a thin blood film. The patient was diagnosed with babesiosis caused by *Babesia microti.* Trophozoites often are seen as ring forms, some with two chromatin dots. Ring forms have a peripheral location, as with *Plasmodium falciparum,* but their large clear central vacuole and the absence of brown pigment (hemozoin) are characteristic of *B. microti.* A single trophozoite can divide by merogony to generate four merozoites arranged in a tetrad, also known as Maltese cross *(arrow).* Tetrads are rare but pathognomonic of small *Babesia* spp. such as *B. microti* and *B. duncani.* Tetrads also can be seen in human red blood cells infected with *B. divergens* or *B. venatorum. (Courtesy Dr. J. Vyas.)*

(WA1, CA5) and *B. duncani*–type (WA2, CA6) organisms cluster separately from other patient isolates (CA1–CA4) and those of wildlife roaming in the same habitat.[77] The third clade contains *Theileria* spp. only. The fourth clade contains *B. divergens* isolates from cattle in Europe, but also *B. divergens*–like organisms from patients in the United States; *B. odocoilei,* which infects white-tailed deer in the United States; and *B. venatorum* isolates from patients in Europe and China.[43,54,62] The fifth clade contains *Babesia* spp. that infect ungulates but rarely humans. These include *B. bovis* and *B. bigemina,* parasites of cattle, as well as *B. crassa* and *B. caballi,* which infect sheep and horses, respectively. Piroplasms of the fourth and fifth clades are *Babesia* spp. sensu stricto.

Long regarded as a single species, *B. microti* is a species complex. The internal topology of this complex was refined by analysis of the gene encoding the η subunit of the chaperonin-containing *t*-complex polypeptide 1 (CCTη).[65] The number, position, and length of introns, as well as the nucleotide-based and amino-acid–based phylogenies, all concur to indicate that the *B. microti* species complex consists of four lineages (US-type, Munich, Kobe, and Hobetsu) and that these four lineages correspond to four separate species.

Whole-Genome Analysis

The genomes of *B. microti*, *B. divergens,* and *B. bovis* have been fully sequenced.[72,78,79] Each genome consists of four nuclear chromosomes, a linear mitochondrial genome, and a circular apicoplast genome. The nuclear genome of *B. microti* is the smallest (6.7 Mb vs. approximately 8 Mb for *B. bovis* and approximately 10 Mb for *B. divergens*). It is notable for the absence of a large family of *ves*-like genes that, in *B. bovis,* encode variant erythrocyte surface antigens (VESAs). VESAs mediate the sequestration of infected erythrocytes in the vasculature. The four *ves*-like genes present in the *B. microti* genome are not arranged in tandem and most likely are not expressed, hence the lack of cerebral manifestations in babesiosis caused by *B. microti. Babesia divergens,* a species with numerous *ves*-like genes, does not evoke cerebral manifestations because the encoded VESA proteins lack the cysteine-rich domains critical for cytoadhesion of infected erythrocytes.

Genome-wide analysis of single nucleotide polymorphisms among *B. microti* isolates obtained from ticks and humans in the United States revealed strong population structure with deep divergence between the Midwest and the Northeast.[80,81] Within the Northeast, three clusters were identified. The first cluster is found on Nantucket, an island 30 miles off Cape Cod. The second cluster encompasses the Northeast mainland except Cape Cod. The third cluster stretches from Cape Cod to the nearby Martha's Vineyard island. The first and second clusters are closely related, whereas the third cluster emerged earlier. Despite the close geographic proximity of these clusters, there is little evidence of genetic recombination.[80] This strong population structure is consistent with the low dispersal capability of *B. microti* that is imposed by the short-range migration of *P. leucopus,* the primary reservoir host. Unlike the Nantucket cluster, the Northeast mainland population presents genetic evidence of recent demographic expansion, possibly from west to east.[80,81] The cluster that spans from Martha's Vineyard to Cape Cod may correspond to a relictual (surviving) population that was maintained in its enzootic cycle by *Ixodes muris* or *Ixodes angustus* prior to the arrival of *I. scapularis.*[80] Whether these distinct *B. microti* populations differ by the number or severity of symptoms they evoke, or both, is unknown.

CLINICAL MANIFESTATIONS

Babesia microti Infection

Symptoms typically appear 1 to 4 weeks after the bite of an infected tick, but 3 to 7 weeks when the infection is transmitted through blood transfusion (median interval, 37 days; range, 11–176 days).[1,17] Most patients experience a gradual onset of fatigue, weakness, or malaise or a combination of these, followed within days by fever and one or more of the following: chills, sweats, headache, myalgia, and anorexia.[1] Fever is intermittent or persistent and has reached 40.9°C (105.6°F). Less frequent symptoms include arthralgia, neck stiffness, nonproductive cough, sore throat, nausea/vomiting, weight loss, and emotional lability. Photophobia, conjunctivitis, joint swelling, diarrhea, and crampy abdominal pain are rare. Dark urine raises the suspicion of severe hemolytic anemia, and may be accompanied by shortness of breath.

On physical examination, fever is the salient feature.[1] The skin may be pale or yellowish. A local red rash can mark the tick bite site; an erythema migrans rash is diagnostic of intercurrent Lyme disease.[4] Ecchymoses and petechiae are rare. Examination of the mouth is unremarkable except when a slight pharyngeal erythema is noted. Scleral icterus is consistent with severe hemolytic anemia. Retinopathy with splinter hemorrhages and retinal infarcts have been reported. Tenderness of the upper left quadrant suggests splenomegaly and may be accompanied by hepatomegaly. Abdominal pain or unexplained hypotension with increased heart rate raises the suspicion of splenic rupture and hemoperitoneum. Splenic rupture with or without palpable splenomegaly has been reported.[82,83] Splenic infarction and subcapsular hematoma may develop in the absence of splenic rupture. Splenic infarction and splenic rupture are confirmed by computed tomography.

Severe babesiosis requires hospital admission.[5,28–30] Of the cases reported to the CDC from 2011 to 2014, one-half were admitted at least overnight.[3] Of those for which the length of hospitalization was documented, one-half had a hospital stay of 3 to 5 days (range, 1–39 days). In smaller case series, the median length of stay typically has ranged from 5 to 9 days, with one patient remaining in the hospital for 100 days.[5,7,28–30,32] Two-thirds of cases are diagnosed in persons 50 to 79 years of age, with the largest number occurring in people 60 to 69 years of age.[3] Patients who are admitted to the hospital are older (median age, 68 years) than those who are not admitted (median age, 58 years).[2] Although age is a risk factor for hospitalization, it is not a risk factor for severe babesiosis.[9,29,30] This finding is best explained by the fact that comorbidities and immunosenescence are not strict correlates of chronologic age. Asplenia and autoimmune disorders predispose to severe babesiosis and therefore hospital admission.[29] Among clinical features, nausea/vomiting and diarrhea are strong predictors of hospitalization.[29]

Severe babesiosis can lead to complications. Pulmonary edema and acute respiratory distress syndrome are most common, followed by congestive heart failure and renal failure.[5,7,28–30,32] Disseminated intravascular coagulation, shock, and splenic rupture are rare. In earlier case series, when clindamycin plus quinine was the mainstay of therapy, death occurred in 6% to 9% of hospitalized patients.[28,30] Of the 10,305 Medicare recipients who received a diagnosis of babesiosis between 2006 and 2013, 1% died within 30 days.[84] Among inpatients, the 30-day mortality rate was 3%. In this series, atovaquone plus azithromycin was

the mainstay of therapy, whereas clindamycin plus quinine was used to treat one-fourth of patients. Death is more frequent (approximately 20%) among immunocompromised patients.[32] Of the TTB cases caused by *B. microti* until fiscal year 2016, one-tenth ended in death.[16,17,21]

Babesia duncani Infection

The eight documented cases caused by *B. duncani* were moderate to severe.[37–41] All but one had one or several comorbidities. Clinical manifestations were similar to those of *B. microti.* Of the five patients who presumably acquired the infection via tick bite, two had a complicated course.[38] One died of cardiopulmonary arrest despite antimicrobial therapy, transfusion, and hemodialysis. The other experienced disseminated intravascular coagulation, pulmonary edema, and renal insufficiency but recovered following antimicrobial therapy and exchange transfusion. The three cases acquired via blood transfusion were severe. One was so anemic that packed RBCs were transfused before diagnosis.[39] Another, a neonate, developed severe respiratory distress.[40] The third developed acute renal failure requiring hemodialysis.[41] All three patients recovered following standard antimicrobial therapy. The implicated blood donors were unaware of their babesial infection but recalled experiencing nausea, fatigue, or a mild flulike illness.

Babesia divergens Infection

Most cases caused by *B. divergens* infection occur in asplenic patients, and are severe.[47] Symptoms tend to appear abruptly 1 to 3 weeks following a tick bite, and consist of persistent high fever (40°C–41°C [104°F–105.8°F]), headache, shaking chills, drenching sweats, myalgia, and lumbar and abdominal pain. Dark urine and jaundice are consistent with severe hemolytic anemia. Without immediate treatment, a shocklike syndrome can develop, with renal failure and pulmonary edema. Once a fatal disease, symptomatic *B. divergens* infection is now successfully managed with exchange transfusion as an adjunct to antimicrobial therapy. *B. divergens* rarely causes disease in spleen-intact individuals. One such case was mild and resolved without adequate antimicrobial therapy.[85] Another case was severe and relapsed despite standard antimicrobial therapy, but eventually resolved after extended therapy with an alternative regimen.[86] Cases of *B. divergens*–like infection in the United States have been severe. All six patients had been splenectomized and three died despite medical intervention.[42–45]

Babesia venatorum Infection

B. venatorum causes mild to severe illness. All five cases in Europe occurred in splenectomized patients.[52–54,86a] One patient was markedly fatigued and produced dark urine.[54] Another patient experienced fever (39°C), chills, headache, jaundice, and dark urine. He recently had begun chemotherapy for diffuse large B-cell lymphoma. The third patient had been treated with rituximab for relapsing Hodgkin disease, and presented with weakness, shortness of breath, and lethargy.[53] He was hospitalized for severe anemia and tested positive in the direct Coombs test, as sometimes seen in babesiosis. He was initiated on prednisolone for presumptive autoimmune hemolytic anemia, which likely worsened the illness. The fourth patient was admitted for recurrent fever, hemolysis, and acute renal failure.[52] He too had been treated with prednisolone for suspected autoimmune hemolytic anemia. The fifth patient was admitted for fever, myalgia, and dark urine. His history included idiopathic thrombocytopenic purpura, bouts of hemolytic anemia, and administration of rituximab 2 years earlier. He was treated with cyclosporine, prednisolone, human immunoglobulin, and a series of antimicrobial agents, including co-trimoxazole (trimethoprim-sulfamethoxazole). The diagnosis of babesiosis was made 2 months later, during a third hospital stay for fever and rigors. Co-trimoxazole, which was curative in a mild case of *B. divergens* infection, may have prevented the progression into severe disease. Despite a large spectrum of clinical severity, symptoms in the five European patients resolved following standard or extended antimicrobial therapy without exchange transfusion. A report from northeastern China indicated that *B. venatorum* causes disease in two-thirds of spleen-intact individuals.[62] Symptoms were those evoked by *B. microti,* although fever, fatigue, chills, and myalgia were experienced by fewer patients. Of the 32 symptomatic individuals, 7 were admitted for irregular fever as high as 40°C. The median length of stay was 16 days (range, 11–20 days). Only 4 patients received appropriate antibiotic therapy (although clindamycin monotherapy), but all 32 patients recovered.

PATHOGENESIS

Erythrocyte Clearance and Rupture

Continuous clearance of *Babesia*-infected RBCs and uninfected RBCs by phagocytes that reside in the red pulp of the spleen contributes to splenomegaly and splenic rupture,[87] and can lead to hemophagocytic lymphohistiocytosis, a fatal condition.[88] As the immune response unfolds, inflammatory cytokines are produced. By suppressing erythropoiesis, interferon-γ (IFN-γ) and interleukin-6 likely contribute to severe anemia. Persistent anemia, despite parasite clearance, has been attributed to autoantibodies that target RBCs.[89] Egress of merozoites is accompanied by erythrocyte rupture and hemoglobin release into the bloodstream. Hemoglobin is rapidly complexed by haptoglobin; minute amounts of free hemoglobin, however, are sufficient to promote systemic inflammation.[90]

Inflammatory and Immune Response

The spleen is the immunodominant organ in babesiosis.[1] This feature, along with the clearance of parasitized RBCs, explains why asplenia is a major risk factor for severe babesiosis.[29] Another key risk factor for severe babesiosis is a low $CD4^+$ T-cell count, as seen in HIV/AIDS patients and allograft recipients.[32,33,35,36] In mice infected with *B. microti,* depletion of $CD4^+$ T cells, a major source of IFN-γ, or neutralization of IFN-γ is sufficient to break host resistance and prevent parasite clearance.[91,92] While central to host immunity, cytokines likely contribute to clinical manifestations. For example, circulating TNF-α and interleukin-6 are elevated during acute illness with *B. microti,*[93] and likely fuel the triad of symptoms consisting of fever, chills, and sweats. Cytokines may also contribute to complications. Mice infected with *B. duncani* die from pulmonary edema associated with intravascular margination of leukocytes. TNF-α is localized to the alveolar septa, whereas IFN-γ is expressed by cells around and within pulmonary vessels.[94] In this model, TNF-α blockade promotes survival, whereas IFN-γ receptor blockade promotes death.[95,96] Although nearly every immunocompetent patient infected with *B. microti* has a positive serology at diagnosis, a role for antibodies is uncertain, as demonstrated in mice.[91] Patients who are or were recently treated with rituximab are prone to persistent or relapsing babesiosis or both,[32,97–99] indicating that B cells, and most likely antibodies, are key to clearing *B. microti* parasites in some immunocompromised hosts.

DIAGNOSIS

A diagnosis of babesiosis should be considered for patients who experience typical symptoms of babesiosis and may have been exposed to ticks in an endemic area between late spring and early fall or who have received blood components, particularly packed RBCs, in the past 6 months.[1] Given that *I. scapularis* transmits *B. microti, B. burgdorferi,* and *Anaplasma phagocytophilum* in the Northeast and upper Midwest of the United States, babesiosis should always be suspected in patients diagnosed with Lyme disease or human granulocytic anaplasmosis in these regions, particularly if symptoms worsen or do not abate within days to weeks of appropriate antibiotic therapy.[4,100]

Routine Laboratory Findings

Routine laboratory tests provide clues. Anemia is evident on a complete blood count (low RBC count, low hematocrit, and low hemoglobin), and often accompanied by an elevated reticulocyte count.[1] The white blood cell (WBC) count is usually normal to slightly decreased, but sometimes elevated.[29,30] A differential may reveal neutropenia as seen in one-third of adults and three-quarters of neonates.[101] A severe thrombocytopenia often precedes severe anemia. Elevated blood levels of lactate dehydrogenase and total bilirubin are consistent with hemolytic anemia, findings that are substantiated by a depressed haptoglobin level. Elevated levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase indicate hepatocyte injury, whereas elevated

aspartate aminotransferase levels without elevated alanine aminotransferase levels are consistent with hemolysis. Severe hemolysis is associated with excess urobilinogen, but rarely with hemoglobinuria. Elevated levels of blood urea nitrogen and serum creatinine denote renal compromise. The direct Coombs test may be positive on admission or in follow-up or both,[52,53,89] implicating autoantibodies as contributors to the anemia. Autoantibodies against platelets can be induced, leading to immune thrombocytopenia.[102] In asplenic patients, babesiosis has reactivated or provoked an Evans syndrome.[103]

A study of 34 patients admitted to a hospital on Long Island, NY, reported that severe anemia (hemoglobin <10 g/dL) is a strong risk factor for complications as a whole, and that high-grade parasitemia (≥10%) is marginally associated with disseminated intravascular coagulation.[28] A review of 139 cases that occurred in New York State between 1982 and 1993 indicated that elevated alkaline phosphatase levels (>125 U/L) and elevated WBC counts ($>5 \times 10^3/\mu L$) are strong predictors of severe outcome, defined as hospitalization longer than 2 weeks, stay in an intensive care unit longer than 2 days, or death.[30] A review of 128 cases diagnosed at Marshfield Clinic in Wisconsin between 1999 and 2015 identified total bilirubin levels greater than 1.9 mg/dL as a strong predictor of severe disease, defined as admission to the intensive care unit; an illness complicated by heart failure, shock, or splenic rupture; or the need for intubation or exchange transfusion.[29] In this study, high-grade parasitemia (>10%), elevated creatinine levels (>1.2 mg/dL), and elevated WBC counts ($>10 \times 10^3/\mu L$) were moderate predictors of severe illness, whereas low WBC counts ($<5 \times 10^3/\mu L$) were highly predictive of severe disease.[29]

Microscopy

Microscopic examination of Giemsa-stained thin blood smears has long been used to make a definitive diagnosis of babesiosis.[1,47,54,77] *B. microti* trophozoites appear round, oval, or ameboid (see Fig. 281.2). The ring form is most common, with one or two red chromatic dots and a light blue cytoplasm. Tetrads of merozoites arranged in a Maltese cross are rare, but pathognomonic of *B. microti* and *B. duncani*. *B. divergens* and *B. venatorum* merozoites appear as paired piriforms but may form tetrads in human RBCs. The analytic sensitivity of microscopy (approximately 0.01% parasitemia as evaluated by highly experienced laboratory personnel) is sufficient in most cases because initial parasitemia typically ranges from 0.05% to 10% in spleen-intact patients, and even higher in asplenic patients (30%–50%, with one case at 85%). When parasitemia is high, extracellular *B. microti* merozoites, either single or in clumps, can be observed. *Babesia* rings resemble early-stage *P. falciparum* trophozoites but lack the brownish deposit (hemozoin) typical of older rings of *P. falciparum*. Gametocytes and schizonts are not observed in babesiosis.

Nucleic Acid Amplification

When *Babesia* organisms are not identified on smear but babesiosis is suspected, amplification of the parasite 18S rRNA gene is recommended. PCR assays that use a fluorescent probe can detect as few as 1 to 5 parasites per microliter of blood, that is, as low as 0.0001% parasitemia.[104–106] Often qualitative, PCR testing provides little help in predicting the course of disease. By use of species-specific primers or probes, real-time PCR assays are well-suited for speciation of the causative organism. The CDC now uses a real-time PCR assay to identify *B. microti* in human blood.[107] This assay, although less sensitive than others, can detect *B. microti* isolates from all four lineages (US-type, Munich, Kobe, and Hobetsu) of the species complex. In patients who experience acute babesiosis caused by *B. microti* in the United States, the persistence of babesial DNA correlates with the persistence of symptoms and is shortened by antimicrobial therapy.[31]

Serology

The caveat of serologic testing is that IgG titers can be low or negative at time of presentation, and typically persist beyond parasite clearance.[1] An indirect fluorescent antibody (IFA) test to detect *B. microti*–specific IgG in serum or plasma can be ordered from commercial laboratories. A titer of 1:64 or greater is considered positive. Titers of 1:1024 or greater indicate active or recent infection. Following acute illness, titers slowly wane over 6 to 12 months.[31] Serology is not practical for *B. divergens* infection because the incubation period is short and the infection fulminant.[47] Sera that react with *B. microti* antigen do not cross react with *B. divergens* or *B. duncani* antigen and vice versa.

THERAPY

Asymptomatic *Babesia microti* Infection

Asymptomatic carriers need not be treated because they typically are immunocompetent and clear the infection within 1 year.[16] Should they become at risk of severe babesiosis during this period (see "Risk Factors" earlier), treatment is recommended. At present, asymptomatic carriers often are identified during investigational product-release testing at selected blood drives. Their numbers will significantly increase once a systematic screening of the blood supply is instituted.

Mild *Babesia microti* Infection

Mild babesiosis caused by *B. microti* is treated with oral atovaquone plus oral azithromycin for 7 to 10 days.[108] Clindamycin plus quinine was the first regimen to demonstrate efficacy against *B. microti*; quinine, however, is poorly tolerated and often interrupted. A prospective, nonblinded, randomized clinical trial demonstrated that atovaquone plus azithromycin is as effective as clindamycin plus quinine in resolving symptoms of babesiosis and clearing *B. microti* parasites.[109] Importantly, untoward drug reactions were noted in fewer of the patients treated with atovaquone plus azithromycin (15% vs. 72% for clindamycin plus quinine).[109] Regimens for adults and children are provided in Table 281.1. Symptoms usually abate within 48 hours following initiation of antimicrobial therapy, and resolve within 1 to 2 weeks. Fatigue may persist for a few months. Low-grade parasitemia can persist for as long as 3 months, but follow-up PCR testing is not recommended because immunocompetent patients eventually clear the infection. Symptoms can recrudesce should a malignancy develop or an immunosuppressive regimen be administered before complete parasite clearance.[31]

Severe *Babesia microti* Infection

First-Line Antimicrobial Therapy

Severe babesiosis caused by *B. microti* should be treated with oral atovaquone plus intravenous azithromycin. Based on cumulative clinical experience, it has long been recommended that severe babesiosis be treated with intravenous clindamycin plus oral quinine.[108] Quinine, however, has frequent and often severe side effects (cinchonism) and cardiotoxicity. No prospective study has compared the two regimens for severe *B. microti* illness, but a retrospective study of 40 patients admitted for babesiosis, including 11 admitted to intensive care, found that all patients but one resolved the infection while on atovaquone plus azithromycin.[110] Regimens for adults and children are provided in Table 281.1. Intravenous azithromycin should be initiated at 500 mg/day.[100] Hematocrit, platelet count, parasitemia, liver enzymes, and renal function should be monitored daily until symptoms abate and parasitemia is reduced (<4%). Thereafter, for patients who are immunocompetent and have a functional spleen, azithromycin can be prescribed orally and the dosage reduced to 250 mg/day.[100] In such patients, atovaquone plus azithromycin typically is administered for a total of 7 to 10 days. Duration, however, should be extended if symptoms persist. The approach to severely immunocompromised patients and asplenic patients is discussed separately (see later).

Adjunctive Exchange Transfusion

Partial or complete RBC exchange transfusion should be considered for patients with high-grade parasitemia (≥10%) or severe anemia (hemoglobin <10 g/dL) in the context of parasitemia.[108] RBC exchange transfusion reduces parasitemia, corrects anemia, and removes inflammatory mediators and toxic by-products of RBC lysis (e.g., hemoglobin). Prompt use of RBC exchange transfusion is associated with favorable outcome.[111] A 90% reduction in parasitemia has been recommended as a target of apheresis and can be achieved by transfusion of a volume of allogeneic RBCs that amounts to 2.5 times the estimated volume of recipient RBCs.[111] When parasitemia is less than 10% and hemoglobin is 10 g/dL or greater, one should take into account the degree of systemic illness; acute respiratory distress syndrome and a systemic inflammatory

TABLE 281.1 Treatment of Human Babesiosis

SPECIES	ILLNESS	HOST[a]	FIRST-LINE REGIMEN[b]	ALTERNATIVE REGIMEN[b]
Babesia microti	Mild		Atovaquone 750 mg q12h PO plus azithromycin 500 mg PO on day 1 and 250 mg/d PO from day 2 on; for 7–10 d[d]	
	Severe[c]	Immunocompetent	Atovaquone 750 mg q12h PO plus azithromycin 500 mg/d IV[e,f]; for 7–10 d[d]	Clindamycin 600 mg q6h IV plus quinine 650 mg q6–8h PO[f,g,h,i]; for same duration
		Immunocompromised and/or asplenic	Atovaquone 750 mg q12h PO plus azithromycin 500 mg/d IV[j]; for at least 6 consecutive wk, including 2 final wk during which parasites are no longer detected on blood smear[k,l]	Atovaquone 750 mg q12h PO plus clindamycin 600 mg q6h IV with or without azithromycin 500 mg/d IV[m,n]; for same duration
Babesia divergens	Mild	Immunocompetent	Clindamycin 600 mg q8h PO plus quinine 650 mg q6–8h PO; for 7–10 d[d,h]	Atovaquone 750 mg q12h PO plus azithromycin 500 mg PO on day 1 and 250 mg/d PO from day 2 on; for 7–10 d[d,n]
	Severe	Immunocompromised and/or asplenic	Immediate complete RBC exchange transfusion combined with clindamycin 600 mg q6h IV plus quinine 650 mg q6–8h PO; for 7–10 d[d,h]	

[a]Dosages are provided for treatment of adults. For pediatric cases, consider using atovaquone 20 mg/kg q12h PO (up to 750 mg/dose) plus azithromycin 5–10 mg/kg PO (up to 250–500 mg/dose), *or* clindamycin 7–10 mg/kg q6–8h IV or PO (up to 600 mg/dose) plus quinine 8 mg/kg q8h PO (up to 650 mg/dose).
[b]Atovaquone is available in a suspension form, and should be taken with dietary fat to increase absorption.
[c]Consider partial or complete RBC exchange transfusion in cases of high-grade parasitemia (≥10%), severe anemia (hemoglobin <10 g/dL), or organ (pulmonary or renal) compromise.
[d]Duration may be extended if symptoms other than fatigue linger.
[e]Intravenous azithromycin may be replaced with oral azithromycin (250–500 mg/day) once the patient has improved.
[f]Recommended for the treatment of severe babesiosis in hospitalized patients.
[g]Intravenous clindamycin may be replaced with oral clindamycin (600 mg q8h) once the patient has improved.
[h]Because quinine carries a risk of QT segment prolongation and torsade de pointes, patients should be monitored by electrocardiography. In the setting of hepatic or renal disease, quinine serum levels should be monitored.
[i]If cardiac toxicity or untoward adverse effects occur, quinine can be replaced with oral atovaquone (750 mg q12h).
[j]Intravenous azithromycin can be replaced with oral azithromycin (500 mg/d) once the patient has improved. Higher doses of oral azithromycin (600–1000 mg/d) accelerate symptom resolution and parasite clearance.
[k]Blood smear is recommended to monitor resolution of infection in severely immunocompromised patients, but recent case reports support the use of a real-time polymerase chain reaction assay to ensure complete parasite clearance.
[l]Duration may vary. In a patient who had been treated with rituximab, parasite clearance was achieved after 27 months of uninterrupted antimicrobial therapy. If asplenia is the only comorbidity, antimicrobial therapy may be shortened as long as clinical cure and parasite clearance are achieved in less than 4 weeks.
[m]Prolonged administration of clindamycin places the patient at risk of *Clostridioides difficile* (formerly *Clostridium difficile*) infection.
[n]Atovaquone can be replaced with atovaquone-proguanil. Atovaquone-proguanil should be taken with dietary fat, but should not be given to patients with severe renal impairment.
IV, Intravenously; *PO,* orally; *RBC,* red blood cell.

response–like syndrome are indications for apheresis.[112] RBC exchange transfusion also is recommended for patients with renal compromise.[108]

Alternative Antimicrobial Regimens

In patients who do not improve clinically within 48 hours of treatment with atovaquone plus azithromycin, intravenous clindamycin plus oral quinine should be considered.[100,108] An alternative regimen can consist of intravenous clindamycin plus oral atovaquone with or without intravenous azithromycin, a regimen favored by the authors.[112] Once the patient has improved, antibiotics can be administered orally.[5,97] Atovaquone-proguanil has been added to azithromycin or various two- or three-drug regimens, particularly when symptoms persisted or relapsed.[36,97–99,112] In an AIDS patient, high-grade parasitemia resolved following addition of atovaquone-proguanil to a four-drug regimen that consisted of azithromycin, atovaquone, clindamycin, and quinine; an asymptomatic recurrence was treated with atovaquone-proguanil monotherapy.[33] Doxycycline is prescribed for intercurrent Lyme disease but has yet to be shown effective against *B. microti.*

Severely Immunocompromised Patients

A retrospective case-control study conducted more than 10 years ago provided the first evidence that severely immunocompromised patients, particularly those who are or were recently treated with rituximab for B-cell lymphoma, are at risk of relapsing babesiosis and should be treated with antimicrobial therapy for at least 6 consecutive weeks, including 2 final weeks during which parasites are no longer seen on blood smear.[32] Given that no particular drug regimen is superior to another,[32] the first-line regimen can consist of oral atovaquone plus intravenous azithromycin. Regimens for adults and children are provided in Table 281.1. Intravenous azithromycin should be initiated at 500 mg/day.[100] Hematocrit, platelet count, parasitemia, liver enzymes, and renal function should be monitored daily until symptoms abate and parasitemia is reduced (<4%). Thereafter, azithromycin can be administered orally but the dosage should be no less than 500 mg/day because lower dosages may promote antibiotic resistance.[99,100] Higher dosages of oral azithromycin (600–1000 mg/day) can be considered because they accelerate resolution of fever and clearance of parasites,[113] thereby minimizing the risk of microbial relapse. Once the patient is no longer critically ill, laboratory testing can be performed every 2 to 3 days until antimicrobial therapy is completed. Close clinical follow-up is recommended.

The approach to treatment outlined for B-cell lymphoma patients extends to any patient who is or was recently treated with rituximab for autoimmune disorders, including rheumatoid arthritis, Evans syndrome, and confirmed or presumptive autoimmune hemolytic anemia.[29,32,97,98] Time from last dose of rituximab to seroconversion and parasite clearance appears to be approximately 18 months.[97] This finding is consistent with the observation that patients who ended rituximab therapy as far as 18 months prior to a diagnosis of babesiosis are at risk of relapsing babesiosis should a standard course of antimicrobial therapy be administered.[32] A prolonged antimicrobial therapy is also recommended for patients with X-linked agammaglobulinemia or low $CD4^+$ T-cell counts due to HIV/AIDS, as well as patients who receive chronic immunosuppressive medication for malignancy, stem cell or solid organ transplantation, or autoimmune disorders.[29,32,100] Reduction or interruption of such immunosuppressive regimens, when possible, is desirable.

Blood smear is recommended to monitor parasite clearance in severely immunocompromised patients.[32] Recent case reports, however, stress the benefit of using real-time PCR to detect low-grade parasitemia.[97,98] A premature interruption of antimicrobial therapy due to apparent cure has led to the emergence of microbial resistance to atovaquone and azithromycin.[99] Such resistance has been associated with missense mutations in the mitochondrial cytochrome b gene (*cytb*) and the apicoplast-encoded ribosomal protein subunit L4 gene (*rpl4*), respectively.[81]

Asplenic Patients

Asplenic patients account for at least one-half of reported cases of relapsing babesiosis.[29,32] Asplenic patients, particularly when presenting with comorbidities that impair the immune response to *B. microti*

parasites, should be treated with prolonged antimicrobial therapy.[32] If asplenia is the only comorbidity, therapy may be shortened to less than 6 weeks as long as clinical cure and parasite clearance are achieved in less than 4 weeks. Given the importance of the spleen for host resistance to *Babesia* parasites, a nonsurgical management of splenic rupture is preferred when the patient is at risk of tick exposure in areas endemic for babesiosis.[82,87]

Infection With Other *Babesia* Species

Symptomatic *B. duncani* infection typically has been treated with intravenous clindamycin plus oral quinine.[37–41] One patient developed a diffuse urticarial rash attributed to quinine, and was cured while receiving intravenous clindamycin monotherapy.[37]

In Europe, symptomatic *B. divergens* infection in asplenic patients is managed with immediate, complete RBC exchange transfusion followed by intravenous clindamycin plus oral quinine.[47] Although used empirically, quinine may provide little to no benefit as demonstrated by its lack of activity in vitro against *B. divergens*[114] and the full recovery by two asplenic patients despite premature interruption of quinine. A splenectomized individual who had a low $CD4^+$ T-cell count due to HIV infection resolved a severe *B. divergens* infection while treated with atovaquone plus azithromycin.[115] A relapse of babesiosis in a spleen-intact individual was treated successfully with atovaquone-proguanil plus azithromycin.[86] In the United States, cases of *B. divergens*–like infections typically have been treated with intravenous clindamycin plus oral quinine or quinidine.[42–45] Quinidine is no longer available in the United States.

Two of the European cases of *B. venatorum* infection were successfully treated with intravenous clindamycin, alone or in combination with oral quinine.[54] A third case was treated with oral clindamycin plus oral quinine but the latter had to be interrupted.[53] Four weeks after clindamycin monotherapy ended, symptoms and parasitemia relapsed. Symptoms quickly resolved following initiation of oral atovaquone plus oral azithromycin, but low-level parasitemia persisted despite 11 weeks of therapy. To avoid relapse, atovaquone monotherapy was prescribed for 6 months until seroconversion and parasite clearance were noted. A pediatric case of mild *B. venatorum* infection in China was successfully treated with oral atovaquone plus oral azithromycin.[61] Symptoms resolved in 3 days, and parasites cleared within 30 days.

PREVENTION

Despite the rise of transfusion-transmitted babesiosis, protection of the blood supply has relied unsatisfactorily on the permanent deferral of blood donors with a history of symptomatic babesiosis.[15,19,21] In March 2018, the FDA approved a nucleic acid test and an arrayed fluorescent immunoassay for the detection of *B. microti* DNA and *B. microti* antibody in human whole blood and human plasma, respectively. These two tests, when combined, hold promise of dramatically reducing the incidence of TTB caused by *B. microti* in endemic areas, and possibly across the United States.[16] In January 2019, the FDA approved the use of another nucleic acid test that is highly sensitive as it detects transcripts of the *B. microti* 18S rRNA gene (rather the gene itself).

Individuals at risk of severe babesiosis (e.g., asplenic and immunocompromised individuals) should avoid areas endemic for *Babesia* spp. from May through September when ticks seek blood.[1] Strategies for tick avoidance and tick removal, and a review of various acaricides are found at the CDC website (http://www.cdc.gov/ticks/avoid/index.html). No vaccine is available to protect humans from any of the zoonotic *Babesia* spp.

Given the increasing confluence of *Ixodes* ticks, *Babesia* spp., and individuals at risk of severe babesiosis in ever-enlarging areas, clinicians should be increasingly alert to the possibility of this previously arcane disease.

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The complete reference list is available online at Expert Consult.

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