cross-reactivity with *P. vivax* appears to interfere with PCR testing. Clinical features of infected individuals range from respiratory distress, acute renal or multi-organ failure, to shock. Treatments vary depending on disease severity. Infected patients with no complications have been treated with quinine, chloroquine or artemether-lumefantrine. Inraveous quinine, artesunate or a combination of chloroquine-primiquine have proven to be effective treatments for patients with severe disease. Artemisinin has shown be quite effective when used as treatment for both mild and severe forms of malaria due to *P. knowlesi*.

BABESIA SPECIES

As noted, there are numerous species of *Babesia* and, of those, four are known to be of concern regarding transmission to humans. Following an introduction to *Babesia* species that includes a historical perspective and descriptions of the most commonly found morphologic forms, two of the most commonly encountered *Babesia* parasites will be discussed.

Historical Perspective

Apicomplexan parasites belonging to the genus *Babesia* are often seen infecting animals, wild and domestic. Babesial organisms were first described in the 1880s as being responsible for **Texas cattle fever** or **red water fever**; this parasitic infection almost decimated the cattle production industry. However, in recent years, several species have demonstrated an ability to cause illness in humans, who are usually considered as an accidental host. The two babesial organisms most commonly isolated from clinical specimens are *B. microti* (*Theileria microti*) and *B. divergens*; other species have demonstrated an ability to cause disease, but are a rarer occurrence. It is important to point out here that some sources suggest that due to ribosomal RNA comparisons *B. microi* fits more into a related genus known as *Theileria* and thus now call it *Theileria microti*. Until this change is universally accepted in the parasitology community, the current name of *B. microti* will be used in this text.

TABLE 6-6 *Babesia* Species Trophozoite: Typical Characteristics at a Glance

Parameter	Description
Appearance	Resembles a ring form Does not contain Schüffner's, Ziemann's, or Maurer's dots
Ring characteristics when stained with Giemsa	Blue cytoplasmic circle connected with or to red chromatin dot Vacuole usually present

TABLE 6-7 *Babesia* Species Merozoite: Typical Characteristics at a Glance

Parameter	Description
Appearance	Resembles four trophozoites attached by their respective chromatin dots in the shape of a Maltese cross

Morphology and Life Cycle Notes

The typical life history of each of these organisms involves several morphologic forms. However, for the purposes of this text, only the two forms most commonly encountered in human specimens will be discussed, the trophozoite and merozoite. Other morphologic forms are responsible for invading the RBCs, but are generally never seen at the point of laboratory diagnosis.

Trophozoite. The trophozoite (Table 6-6) develops after the sporozoite infects the red blood cell. This form resembles the ring form of *Plasmodium* infections. The typical ring, when stained with Giemsa, consists of a blue cytoplasmic circle connected with or to a red chromatin dot, also referred to by some as a nucleus. The space inside the ring is known as a vacuole. The ring form is the most commonly seen diagnostic feature of babesiosis and can be differentiated from malarial organisms by the absence of malarial pigments (hemozoin) and of Schüffner's, Ziemann's, or Maurer's dots (Table 6-7).

Merozoite. The merozoite develops within the red blood cell as the trophozoite matures. The merozoite resembles four trophozoites attached together by their respective chromatin dots in the

shape of a cross, often referred to as resembling a Maltese cross. Merozoites undergo binary fission in the human host to produce more sporozoites.

Babesiosis has a sexual and asexual phase in its life cycle. The sexual phase occurs within its vector, the tick, and the asexual phase occurs within its host (e.g., mice, deer, cattle, dogs, humans). It is generally transmitted through the bite of an infected tick of the genus *Ixodes*. The uninfected host must be in contact with the tick's saliva for 12 hours or longer before this parasite can be transmitted. The infected tick transmits sporozoites into the uninfected host. The sporozoites invade the red blood cells and develop into trophozoites. Multiple sporozoites can infect a RBC, so multiple trophozoites can be seen within the infected RBC. The trophozoites continue to develop into merozoites. The merozoites mature and develop into gametocytes inside their normal animal host, but are not generally seen in the accidental human host. In the human host, the merozoites undergo binary fission to produce more sporozoites; when the number of sporozoites exceeds the red blood cell's capacity, it ruptures, releasing sporozoites to infect more red blood cells. An ixodid tick bites an infected host and the gametocytes travel to the gut, where they unite to form an ookinete. The ookinete travels to the salivary glands where **sporogony**—the process of spore and sporozoite production via sexual reproduction—takes place, resulting in numerous sporozoites that can be transmitted to a new host.

Quick Quiz! 6-16

Humans are an accidental host of *Babesia* species. (Objective 6-6)
A. True
B. False

Laboratory Diagnosis

Giemsa-stained peripheral blood films are the specimens of choice for the laboratory diagnosis of babesiosis. Wright's stain may also be used and will result in an accurate diagnosis. However, because Giemsa is the recommended stain for all blood films submitted for parasite study, the specific morphologic discussion of *Babesia* is based on the use of this stain. Thick and thin blood films should be made and examined. Thick blood smears serve as screening slides; thin blood smears are used for differentiating *Babesia* from *Plasmodium* spp. All blood films should be studied under oil immersion. Careful and thorough screening of all smears is crucial to ensure the correct identification, reporting, and ultimately the proper treatment of the organisms present. The timing of blood collection for the study of *Babesia* is not crucial to success in retrieving the *Babesia* parasites; they have not shown periodicity, as have the malarial organisms.

In addition to blood films, serologic tests and PCR techniques for babesiosis are available. These tests are generally best used for diagnosing patients with a low parasitemia or in donor blood supply screening and epidemiologic studies. Serologic and PCR testing are also valuable for the speciation of *Babesia,* because this is a limitation of blood film tests. Representative laboratory diagnostic methodologies are described in Chapter 2 as well as within each individual parasite discussion, as appropriate.

Quick Quiz! 6-17

The specimen of choice for the recovery of *Babesia* is: (Objective 6-10)
A. Tissue
B. Cerebral spinal fluid (CSF)
C. Stool
D. Blood

Pathogenesis and Clinical Symptoms of *Babesia*

The typical patient presenting with babesiosis was exposed 1 to 4 weeks prior to the onset of symptoms. Babesiosis is generally a self-limiting infection. Its onset is usually gradual and characterized by prodrome-like symptoms—fever,

headache, chills, sweating, arthralgias, myalgias, fatigue, and weakness. The fever shows no periodicity. Hepatosplenomegaly and mild to severe hemolytic anemia have been recorded. Elevated bilirubin and transaminase levels have also been demonstrated.

Babesiosis tends to be worse for the splenectomized and immunocompromised patient. Rare asymptomatic infections have also been recorded. Infections tend to present in late summer to early fall and generally correlate with the breeding cycle of the ixodid tick. It is also not uncommon to see a patient coinfected with Lyme disease and/or human granulocytic ehrlichiosis.

Quick Quiz! 6-18

Babesiosis is characterized by all the following except: (Objective 6-8)

A. Trophozoites resembling the ring form seen in *Plasmodium* infections
B. A mild to severe hemolytic anemia
C. Fever periodicity
D. None of the above

Babesia Classification

Babesia species belongs to the phylum Apicomplexa, class Aconoidasida, order Piroplasmida, family Babesiidae. The *Babesia* species discussed in this chapter occur in the blood, as indicated in Figure 6-8.

Babesia microti
(baa″beez-ee′yuh/my″crō-tee)

Common associated disease and condition names: Presently, no common name exists.

Babesia divergens
(baa″beez-ee′yuh/di′′vər-jənz)

Common associated disease and condition names: Presently, no common name exists.

Morphology

The morphologic features of *B. microti* and *B. divergens* are described in the general notes concerning babesiosis.

Laboratory Diagnosis

The laboratory diagnostic procedures for identifying *B. microti* and *B. divergens* are described in the general notes concerning babesiosis.

Life Cycle Notes

The life cycle of *B. microti* and *B. divergens* are described in the general notes concerning babesiosis.

Epidemiology

B. microti is commonly found in areas of southern New England, such as Nantucket, Martha's Vineyard, Shelter Island, Long Island, and Connecticut. It has also been isolated in clinical specimens in patients in New Jersey, Wisconsin, Missouri, Georgia, North Carolina, and Mexico. The vector most commonly associated with the transmission of *B. microti* is *Ixodes dammini*. The principal reservoir host for this infection is the white-footed mouse, *Peromyscus leucopus*.

B. divergens is commonly found in European countries, particularly those in the former Yugoslavia, Russia, Ireland, and Scotland. The vector most commonly associated with the transmission

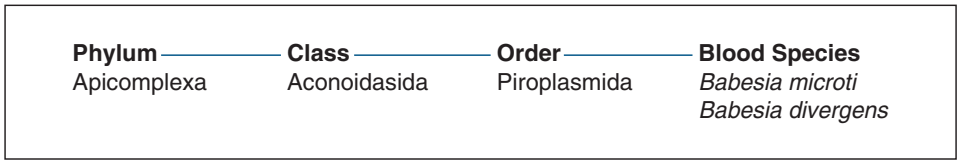

FIGURE 6-8 Parasite classification—*Babesia* species.

of *B. divergens* is *Ixodes ricinus*. The principal reservoir hosts are cattle and rabbits. *B. divergens* has also been described in the Nantucket area, primarily in the rabbits and birds of the region.

Babesiosis has also been demonstrated to be a transfusion-transmissible disease and has the potential to be transmitted congenitally and by the sharing of intravenous drug needles.

Clinical Symptoms

The clinical symptoms for *B. microti* and *B. divergens* infections have been described earlier ("Pathogenesis and Clinical Symptoms"). *B. divergens* tends to be the more severe of the two parasitic infections and is frequently fatal if left untreated. *B. microti* tends to be rather benign and self-limiting. Disease with either of these organisms is often more severe for older adult, immunosuppressed, and/or splenectomized patients.

Treatment

The treatment of babesiosis often involves a combination of drugs. The most common combinations are clindamycin and quinine or atovaquone and azithromycin. Diminazene and pentamidine, in combination or singly, and pyrimethamine and quinine, in combination or singly, have also shown promise, but the side effects of some of these medications may be less than desirable. Patient age, immune status, G6PD status, and other clinical symptoms will play a role in the physician's choice as to which therapy is best for the patient.

Prevention and Control

The best prevention measure is to avoid tick-infested areas. However, examining the body for ticks immediately after leaving such an area and rapid removal of the tick are crucial. The tick must feed for at least 12 hours before it is able to transmit the parasite. Using insect repellents and eradicating the tick population are also helpful for disease prevention and control.

Quick Quiz! 6-19

Which of the following are laboratory diagnostic procedures is recommended for specifically identifying *T. microti*? (Objective 6-10)

A. Thick and thin blood films
B. Serologic testing
C. PCR techniques
D. Both B and C are correct.
E. None of the above

Quick Quiz! 6-20

Which of the following is not a location known for infection by *T. microti*? (Objective 6-2)

A. California
B. North Carolina
C. Mexico
D. Nantucket

Quick Quiz! 6-21

For which patient would babesiosis be more severe? (Objective 6-8)

A. The splenectomized
B. The patient with *Babesia divergens*
C. Older adults
D. All of the above

LOOKING BACK

As with all parasites, the proper identification of malaria and babesiosis is crucial to ensure that the patient is adequately treated when necessary. *Plasmodium* and *Babesia* spp. have morphologic forms that may look similar. However, because not all species typically show all the morphologic forms in the peripheral blood, coupled with the fact that other morphologic forms look different (e.g., mature schizonts, gametocytes) and whether pigment is produced, allow accurate speciation of the malarial organism and differentiation of malaria from babesiosis. Thorough screening of all smears is essential; this practice ensures that even low numbers of organisms will be detected.