



## Babesia gibsoni: An Emerging Pathogen in Dogs

Lindsay Boozer, DVM

Douglass Macintire, DVM, DACVIM, DACVECC

Auburn University

### ABSTRACT:

*Babesia gibsoni* is a tickborne protozoal blood parasite that causes hemolytic anemia, thrombocytopenia, lethargy, and splenomegaly. In the United States, the disease primarily affects American pit bull terriers and is often subclinical. Other breeds of dogs are less often infected and may have a history of fighting with a pit bull terrier. Diagnosis is most often made by identifying the organism on blood smears or through polymerase chain reaction testing. Serologic assays are less sensitive and specific. In many cases, treatment is frustrating, low levels of parasites remain, and a chronic subclinical carrier state develops. Recently, administering a combination of azithromycin and atovaquone has shown encouraging results in treating chronic *B. gibsoni* infections.

Canine babesiosis is a hemoprotozoan infection typically caused by *Babesia canis* or *Babesia gibsoni*. *B. canis*, the larger organism (4 to 5  $\mu$ m), is more common in the United States, especially in the Gulf Coast region and the South (Figure 1). *B. gibsoni* has recently been recognized as an important pathogen that affects dogs in the Middle East, Africa, Asia, Europe, and many areas of the United States.<sup>1-4</sup> Before 1990, *B. gibsoni* infection had been reported only twice in the United States. One infection occurred in a dog imported from Malaysia,<sup>5</sup> and another dog in Connecticut apparently became infected locally.<sup>6</sup> In the 1990s, *B. gibsoni* infection was reported in 11 dogs from California<sup>7</sup> and a group of primarily pit bull terriers from North Carolina.<sup>8</sup> The small *Babesia* sp from California

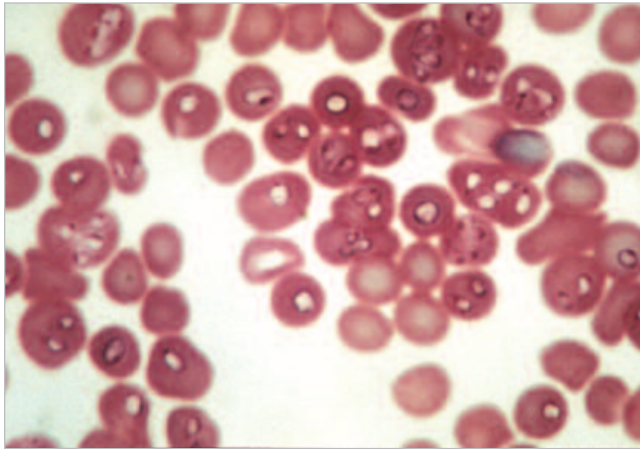
was later determined to be phylogenetically distinct from *B. gibsoni* and is most closely related to *Theileria* spp and *Babesia* isolates from wildlife

and humans in the western United States.<sup>9,10</sup> The *B. gibsoni* that affects dogs in the remainder of the United States is identical to the Asian *B. gibsoni* and is categorized as *Babesia* spp *sensu stricto*.<sup>10</sup> The small *Babesia* sp that affects dogs in Europe appears to be a third species that is most closely related to the human and rodent pathogen *Babesia microti*.<sup>2</sup> *B. gibsoni* infection has now been diagnosed in many areas of the United States and has also been reported in foreign US military bases and surrounding areas.<sup>4</sup>

### PATHOGENESIS

The specific vector of *B. gibsoni* infection in the United States is not well established but is suspected to be *Rhipicephalus sanguineus*, the brown dog tick.<sup>11,12</sup> In other countries, *Haemaphysalis* ticks are also known to transmit *B. gibsoni* infection. Dogs become infected when ticks feed for 2 to 3 days and release sporozoites into the circulation.<sup>1,4</sup> Inside the host, the organisms attach to the red cell membrane and

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**Figure 1.** *B. canis*, the larger *Babesia* organism that affects dogs. This species is easily recognized because of its large size and pyriform shape in canine RBCs.

are engulfed by endocytosis. In the cytoplasm, binary fission occurs, resulting in merozoites. Ticks become infected with merozoites during feeding and may remain infective for many generations through transstadial and transovarial transmission.<sup>4</sup> In experimental infections derived from naturally infected dogs in Oklahoma, parasites were detected 1 to 5 weeks after inoculation.<sup>13</sup> Parasitemia peaked at 1.9% to 6% by 4 to 6 weeks after infection. Easily detectable parasitemia (>0.1%) was present for 3 to 4 weeks.<sup>14</sup> The severity of clinical signs was highly variable and developed approximately 1 to 2 weeks after infection.<sup>14</sup>

After initial parasitemia, the immune system does not totally eradicate the infection, and a chronic carrier state

*B. gibsoni* can cause hyperacute, acute, and chronic infections. Hyperacute infections are rare and primarily occur in puppies, resulting in rapid death. These infections are presumed to be maternally acquired. Acute *B. gibsoni* infections are typically associated with fever, lethargy, thrombocytopenia, and anemia. Chronic infections may be completely asymptomatic or may be characterized by intermittent fever, lethargy, and weight loss. Limited studies suggest that chronic infections, recrudescence, and poor response to therapy may be more common with the Californian isolate than with *B. gibsoni*.<sup>7,14</sup>

Hemolytic anemia is the predominant feature of babesiosis, and thrombocytopenia is also common in infected dogs. Anemia is attributed to extra- and intravascular hemolysis. Mechanisms of RBC destruction include increased osmotic fragility, shortened RBC life span, and erythrophagocytosis. Secondary immune-mediated destruction occurs because of parasite antigens on the RBC surface, parasite-induced membrane damage, and possibly other membrane-associated antigens.<sup>1,4,15,16</sup> Oxidative damage, impaired hemoglobin function, sludging, and sequestration of erythrocytes also likely occur.<sup>1,4,16</sup>

In addition to tickborne transmission, vertical transmission is also suspected, and infections have been identified in a dam and her 3-day-old puppies.<sup>17,18</sup> Transmission can also occur through transfusion of infected blood.<sup>5,19,20</sup> Interestingly, there have been several reports of infections in dogs that have been attacked by pit bull terriers.<sup>21,22</sup> Retrospective evaluation of dogs other than American pit bull terriers diagnosed with *B. gibsoni* infection found that six of 10 dogs had a history

## ***B. gibsoni* infection may closely resemble immune-mediated hemolytic anemia or immune-mediated thrombocytopenia. Positive Coombs' test results are common.**

remains. Relapses may occur months to years later, and long-term sequelae, such as glomerulonephritis or polyarthritis, may develop.<sup>7,13,15</sup> With *B. gibsoni* infection, parasitemia is usually mild, although anemia can be severe (<20% red blood cells [RBCs]). Splenectomized animals may have more severe parasitemia and anemia. The small *Babesia* sp that affects dogs in California tends to cause a greater degree of parasitemia, and infected erythrocytes may approach 40% in some cases.<sup>7</sup>

of being bitten by a pit bull terrier.<sup>22</sup> Although unknown, the mechanism that seems most likely is direct blood-blood contact during fighting. Possible transmission through breeding, nursing, saliva, or swallowing blood has not been evaluated.

### **CLINICAL FINDINGS**

The vast majority of reported cases of *B. gibsoni* infection in the United States have involved American pit



**Figure 2.** Dogs with babesiosis can present with autoagglutination and hemolytic anemia similar to the presenting clinical signs seen with immune-mediated hemolytic anemia.

bull terriers.<sup>8,22,23</sup> Over half (18 of 33) of American pit bulls screened using polymerase chain reaction (PCR) testing in the southeastern United States tested positive for *B. gibsoni*. In 10 of these dogs, organisms were evident on blood smears. Subclinical infection was very common, only one animal was ill during evaluation, and four additional dogs had a history of acute hemolytic anemia.<sup>23</sup> The reason for the strong breed predilection is unknown. Possible factors include vertical transmission,

of spontaneously infected symptomatic dogs.<sup>25</sup> The leukogram changes are nonspecific, although severe transient neutropenia ( $<1,000/\mu\text{l}$ ) was noted in several dogs 1 week after experimental infection with *B. gibsoni*.<sup>14</sup> Marginal neutropenia persisted in some dogs for several weeks.

Moderate to marked thrombocytopenia is very common. In experimental infections, thrombocytopenia developed sooner and persisted longer than parasitemia or anemia.<sup>14</sup> Subclinically infected pit bull terriers demonstrated significantly lower platelet counts, higher mean platelet volumes, and lower hematocrits than did uninfected dogs of various breeds.<sup>23</sup> The mechanism for thrombocytopenia is not well understood. The increased mean platelet volumes suggest bone marrow response to consumption, destruction, or sequestration of platelets. Hyperbilirubinemia is relatively uncommon with *B. gibsoni* infections but may occur more often in severe *B. canis* infections.<sup>4</sup>

## DIAGNOSIS

Diagnosing *B. gibsoni* infection can be challenging because many animals are presumed to have idiopathic immune-mediated anemia or another tickborne disease. Detecting RBC autoagglutination and positive results of a Coombs' test may complicate the diagnosis (Figure 2). Identifying the parasite through blood smear evaluation

***B. gibsoni* frequently causes subclinical infection in American pit bull terriers. For other breeds of dogs that present with *B. gibsoni* infection, owners should be questioned about a history of bite wounds or blood transfusions.**

dogfighting, genetic susceptibility, frequent blood–blood contact, crowded kennel environments, poor parasite control, nutritional factors, and increased awareness. Interestingly, in Okinawa, over 400 cases of *B. gibsoni* infection were diagnosed in a 16-year period. In this case series, there was not a predilection for pit bull terriers, and a variety of purebred and mongrel dogs were infected.<sup>24</sup>

Anemia can be severe, especially in young and immunosuppressed patients. The hemogram typically reveals macrocytic, hypochromic, and regenerative anemia. Coombs' test results may be positive in up to 90%

can be difficult because of the small size of the organism and relatively low levels of parasitemia (Figure 3). *B. gibsoni* is approximately  $1 \times 2.5 \mu\text{m}$  and may have a signet, rod, or cocci shape.<sup>26</sup> A single organism per RBC is common, although multiple forms have been reported. Giemsa- or Wright's-stained fresh blood smears are recommended, and organisms are typically found in the peripheral portion of the blood smear. Serologic assays (i.e., immunofluorescent antibody [IFA] and ELISA) have also been used to detect infection. IFA is expensive, has low sensitivity, and is compromised by cross-reactivity between species. In general,

titers above 1:320 with compatible clinical signs and hematologic findings support a possible diagnosis of *B. gibsoni* infection.<sup>4</sup> Antibody response to babesial infection typically takes 8 to 10 days to develop, and some clinically affected dogs, especially puppies, initially test negative.

PCR testing has recently become available and is very useful in identifying the infective species, detecting low levels of parasitemia, recognizing subclinical infections, and monitoring response to therapy. With PCR testing, species-specific amplification of regions of parasite DNA provides a definitive diagnosis. Seminested PCR can detect levels of parasitemia that are over 1,000 times lower than the approximate 0.001% parasitemia detectable by light microscopy.<sup>27,28</sup> False-negative results may occur when parasitemia levels are very low.<sup>29</sup> The diagnosis of canine babesiosis should be as specific as possible because prognosis and response to treatment are variable.

Coinfection with other tickborne diseases occurs relatively often as a result of transmission of several infectious organisms by a single vector and infestation with multiple species of ticks. *B. canis*, *Ehrlichia canis*, some *Rickettsia* spp, and possibly *Bartonella vinsonii* and *Ehrlichia platys* are transmitted by *R. sanguineus*, the brown dog tick.<sup>30,31</sup> Babesiosis should be considered in dogs that do not respond completely to treatment of other tickborne diseases.<sup>30</sup>

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### **PCR testing is useful in confirming the diagnosis of *B. gibsoni* infection, screening blood donors, detecting chronic infections, and monitoring response to therapy.**

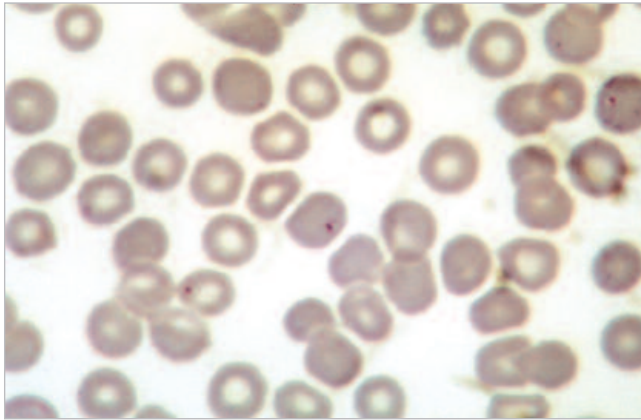
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#### **TREATMENT**

Until recently, dogs were presumed to remain chronically infected with low levels of parasites, even after appropriate treatment.<sup>4</sup> Imidocarb is the only agent licensed for treating babesiosis in the United States and has direct action against the parasite DNA that causes unwinding and denaturation.<sup>15,25</sup> Most *B. canis* infections can be cleared with imidocarb (5 to 6.6 mg/kg IM or SC, repeat in 2 weeks), but small *Babesia* spp are generally more difficult to treat. Imidocarb is less effective in *B. gibsoni* infection: In most cases, the parasites are not totally eliminated. Pain at the injection site and cholinergic side effects (i.e., salivation, urination, diarrhea, vomiting) may occur. Premedication with subcutaneous atropine (0.05 mg/kg) 20 to 30 minutes before imidocarb injection is recommended.<sup>26</sup> Imidocarb also has some efficacy against *E. canis* and may be useful in dual infections.

Diminazene aceturate (berenil; Ganaseg, Novartis Animal Health) is also a relatively effective treatment but is not currently available in the United States. Although doses of 3.5 to 5 mg/kg are often effective in *B. canis* infections, doses of 7.5 to 10 mg/kg are recommended in treating *B. gibsoni*





**Figure 3.** *B. gibsoni* organisms can be easily missed on a blood smear because of their small size and pleomorphic appearance. There is usually a single ringed organism in each infected RBC.

infections.<sup>4</sup> The drug binds to and inhibits parasite DNA synthesis.<sup>15</sup> The most common side effect is pain at the injection site. Serious complications are rare (<0.1%) and include ataxia, seizures, and death.<sup>24</sup> Metronidazole, clindamycin, and doxycycline have some efficacy against the parasite but are not effective in eliminating parasitemia.

More recent investigation into administering atovaquone (13.5 mg/kg PO tid with a fatty meal for 10 days) and azithromycin (10 mg/kg PO q24h for 10 days) in chronic *B. gibsoni* infections shows promising results. The same combination has been used to treat *B. microti* infections in humans and rodents.<sup>32,33</sup> PCR testing has shown that 80% of naturally infected dogs treated with this combination appear to clear the infection and test negative.<sup>29</sup> Side effects did not occur in 11 relatively healthy, naturally infected dogs treated with this protocol.

Atovaquone (Mepron, GlaxoSmithKline) is a naphthoquinone with broad-spectrum antiprotozoal activity against *Plasmodium* spp, *Pneumocystis carinii*, *Toxoplasma* spp, and *Babesia* spp. The drug is structurally similar to the inner mitochondrial protein ubiquinone (coenzyme Q), which is an essential part of electron flow in aerobic respiration. Cytochrome binding is specific for parasite mitochondria. In humans, the drug is highly protein bound (>99%) but does not cause significant displacement of other protein-bound drugs.<sup>34</sup> Coadministering tetracycline can cause a 40% decrease in blood levels but demonstrated a synergistic effect in vitro. There is minimal hepatic or renal elimination, and more than 94% of the drug is excreted in the feces over 3 weeks. In

humans, the most frequent side effects include maculopapular rash, nausea, diarrhea, and headaches in 10% to 35% of patients. Side effects may resolve with continued treatment. Elevations in liver enzymes have also been seen.<sup>34</sup> A major drawback of the atovaquone–azithromycin regimen is the high cost. The cost of atovaquone alone is approximately \$24/day to treat a 55-lb (25-kg) dog. Azithromycin costs approximately \$8/day to treat a 55-lb (25-kg) dog. Two injections of imidocarb for a 55-lb (25-kg) dog cost about \$22. Decoquinate, a chicken anticoccidial drug, is very closely related to atovaquone, is readily available, and may prove useful in treatment. Studies to evaluate the efficacy of decoquinate have not been conducted.

In many cases, supportive care with fluids, blood products, and/or bovine hemoglobin are needed. The use of glucocorticoids is controversial. Glucocorticoids may reduce immune-mediated destruction, but long-term use may reduce splenic clearance of parasites and encourage ongoing infection.<sup>4</sup> We prefer to attempt treatment with supportive care and antiparasite therapy first. Immunosuppressive therapy should be considered only in refractory cases with ongoing hemolytic anemia.

PCR testing can be conducted to assess response to therapy. It has been suggested that when monitoring response to atovaquone–azithromycin therapy, two consecutive PCR tests with negative results should be obtained 2 to 4 weeks apart at least 60 days after treatment. Both drugs have very long half-lives. Serum IFA titers are not recommended for therapeutic monitoring, and antibody titers may persist for months to years.<sup>30</sup>

## PREVENTION

Good tick control is essential in preventing the spread of babesiosis. In addition, preventing dogfighting as well as direct blood contact by using sterilized instruments during tail docking and ear cropping procedures and when administering injections are critical. Good screening measures should be established for potential canine blood donors. Blood smear evaluation, serum antibody titers, and PCR testing for *B. canis* and *B. gibsoni* should be conducted to confirm the diagnosis. Modern diagnostic techniques probably negate the need to splenectomize blood donors. Breeding kennels should implement screening programs, tick control, and quarantine procedures to help prevent the disease from spreading. If a dog that tests positive is found in a kennel, PCR and serologic testing of all other dogs are recommended. Treatment is recommended, even in subclinically infected dogs.<sup>30</sup>

International transportation of dogs should also require mandatory testing, strict parasite control, and appropriate treatment of dogs that test positive.

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### 1. The suspected vector of *B. gibsoni* in the United States is

- a. mosquitoes.
- b. *Haemaphysalis* spp.
- c. seed ticks.
- d. *R. sanguineus*.
- e. fleas.

### 2. The incubation period of *B. gibsoni* infection is

- a. 24 to 48 hours.
- b. 3 to 7 days.
- c. 1 to 3 weeks.
- d. 4 to 6 weeks.
- e. 1 to 3 months.

### 3. Anemia in *B. gibsoni* infections may be attributed to

- a. extravascular and intravascular hemolysis.
- b. increased osmotic fragility.
- c. erythrophagocytosis.
- d. secondary immune-mediated destruction.
- e. all of the above

### 4. Which of the following has not been associated with transmission of *B. gibsoni* infection?

- a. blood transfusion
- b. infective tick bite
- c. vertical transmission
- d. fomites
- e. bite wounds or blood contact

### 5. Which drug has not been used in treating *B. gibsoni* infection?

- a. ivermectin
- b. imidocarb
- c. azithromycin
- d. atovaquone
- e. diminazene aceturate

### 6. The most common side effect of diminazene administration is

- a. anaphylaxis.
- b. seizures.
- c. vomiting.
- d. pain at the injection site.
- e. salivation.

### 7. *B. gibsoni* infection may resemble immune-mediated hemolytic anemia or immune-mediated thrombocytopenia because it can be associated with

- a. highly regenerative anemia.
- b. thrombocytopenia.
- c. positive results from a Coombs' test.
- d. organisms that are difficult to detect.
- e. all of the above

### 8. Which test is best able to differentiate between *B. canis* and *B. gibsoni* infections?

- a. Coombs' test
- b. PCR testing
- c. sedimentation rate
- d. paired titers
- e. serology

### 9. Cholinergic side effects may occur with

- a. diminazene.
- b. imidocarb.
- c. trypan blue.
- d. azithromycin.
- e. atovaquone.

### 10. Which disease does not share a common vector with *B. gibsoni*?

- a. salmon poisoning
- b. *B. canis* infection
- c. *E. canis* infection
- d. *B. vinsonii* infection
- e. All of the above are transmitted by the brown dog tick.