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BABESIOSIS IN DOGS – UPDATE ON PATHOGENESIS, TREATMENT AND PREVENTION

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Babesiosis is caused by protozoal parasites that infect erythrocytes and cause anemia. *Babesia* species are tick-borne apicomplexan parasites that infect a variety of domestic and wild animals and may cause moderate to severe disease. Babesiosis has a worldwide distribution and global importance. Hemolytic anemia with erythrocyte destruction and a systemic inflammatory response account for most of the clinical signs observed in canine and feline babesiosis.

Babesia infection was identified in the past based on the morphologic appearance of the parasite in erythrocytes. All large forms of canine *Babesia* (2.5–5.0 µm) were designated *Babesia canis*, whereas all the small forms (1.0–2.5 µm) were considered as *Babesia gibsoni*. However, the development of molecular methods has demonstrated that more piroplasmid species infect dogs and cause different diseases. *Babesia rossi*, *B. canis* and *B. vogeli* previously considered as subspecies are identical morphologically but differ in the severity of clinical manifestations which they cause, their tick vectors, genetic characteristics, and geographic distributions, and are therefore currently considered separate species. Another yet unnamed large *Babesia sp.* most closely related to *B. bigemina* was found to infect immunocompromised dogs in North America. The small *Babesia spp.* that infect dogs include *B. gibsoni, B. conradae* described from California, and the *B. vulpes* (*B. microti*-like; *Theileria annae*) (Table 1). None of the *Babesia* species that infect dogs has been found to be zoonotic.

The geographical distribution of the causative agents and thus the occurrence of babesiosis are largely dependent on the habitat of relevant tick vector species, with the exception of *B. gibsoni* where evidence for dog to dog transmission indicates that infection can be transmitted among fighting dogs breeds independently of the limitations of vector tick infestation. *Babesia vogeli* and *B. gibsoni* have wide distributions in both the Old and New World continents, whereas *B. rossi* has to date been mostly restricted to Africa and *B. canis* has mostly been reported from Europe.

Dogs are infected when *Babesia* sporozoites are injected with saliva into the host's skin during the blood meal. The parasites invade the erythrocytes and form ring-shaped trophozoites. The parasite replicates within the erythrocyte and forms merozoites observed as pairs of attached pear-shaped parasites in some *Babesia* species. Merozoites may further divide forming 8 or more parasites in the same erythrocyte and eventually destroying the cell freeing into the blood to invade more erythrocytes. Ticks feeding on infected blood take up merozoites and sexual parasite development in the tick gut is followed by sporogony in its tissues. The parasite reaches the tick salivary glands or it's oocytes from which transmission occurs. *Babesia* spp. are transmitted transstadially from one stage in the tick life cycle to another, and also transovarially through the tick eggs, as shown for some *Babesia* spp. *Babesia* infection with some species has also been demonstrated to be transmitted via blood transfusion and transplacentally. Furthermore, several studies have provided evidence that *B. gibsoni* is transmitted directly from dog to dog via bite wounds, saliva, or ingested blood.

Table 1 - Species of *Babesia* that cause canine babesiosis, their geographic distribution, tick vectors, size of merozoites stages and main drugs used for their treatment.

Species	Geographical distribution	Potential or confirmed vectors	Size of merozoite stages in µm	Main drug or drug combination
Babesia canis	Europe	*Dermacentor reticulatus*	2 x 5 (large forms)	Imidocarb dipropionate
Babesia rossi	Southern Africa, Nigeria, Sudan	*Haemaphysalis elliptica* *Haemaphysalis leachi*	2 x 5 (large forms)	Diminazene aceturate; imidocarb dipropionate
Babesia vogeli	Africa, Asia, southern Europe, North, Central and South America, Australia	*Rhipicephais sanguineus sensu lato*	2.5 x 4.5 (large forms)	Imidocarb dipropionate
Large unnamed *Babesia*	Eastern United States	Unknown	2 x 6 (large forms)	Imidocarb dipropionate
Babesia gibsoni	Southeast Asia, United States, Australia, Europe	*Haemaphysalis longicornis* *Haemaphysalis bispinosa?* *R.. sanguineus s.l.?**	1 x 3 (small forms)	Atovaquone and azithromycin; clindamycin and diminazene aceturate and imidocarb dipropionate for atovaquone-resistant strains
Babesia conradae	United States (California)	*R. sanguineus s.l.?*	0.3-3 (small forms)	Atovaquone and azithromycin
Babesia vulpes (Babesia microti-like; Theileria annae)	Europe, North America	*D. reticulatus?* *Ixodes hexagonus?,* *Ixodes ricinus?, Ixodes canisuga?,* *R. sanguineus s.l.?*	1 x 2.5 (small forms)	Atovaquone and azithromycin; bupravaquone and azithromycin

The clinical findings in babesiosis are variable and depend on the *Babesia* species infecting dogs. In general, hemolytic anemia and the systemic inflammatory response syndrome leading to multiple-organ dysfunction syndrome are responsible for most of the clinical signs observed in canine babesiosis. Hemolysis may result in hemoglobinemia, hemoglobinuria, bilirubinemia and bilirubinuria. Thrombocytopenia is consistently observed in babesiosis and may be caused by immune mechanisms, splenic sequestration or coagulatory consumption of platelets from hemolytic or vascular injury. Immune mediated thrombocytopenia has been demonstrated in experimental canine babesiosis caused by *B. gibsoni*.

Tissue hypoxia is found in severe canine babesiosis. It is caused by anemia, hypotensive shock, vascular stasis by sludging of erythrocytes, excessive endogenous production of carbon monoxide, and parasitic damage to hemoglobin. The central nervous system, kidney, and muscle are the organs most affected by tissue hypoxia. Tissue hypoxia, hypertensive shock, multiple organ dysfunction and potential mortality have been documented mostly in association with *B. rossi* and *B. canis* infections. Young pups and immunocompromised adult dogs, such as dogs with hyperadrenocorticism or treated with immunosuppressive therapy, may suffer a severe disease with *B. vogeli* infection.

The spleen has an important function in controlling babesiosis. Experimentally infected splenectomized dogs rapidly develop parasitaemia and clinical disease and may reach high parasitaemia levels. Splenectomy has also been associated with natural canine and human babesiosis.

Detection of *Babesia* in stained blood smears has been the standard diagnostic technique for many years. This method is reliable when a moderate to high parasitaemia is present. However, a direct correlation between the level of *Babesia* parasitaemia and the magnitude of clinical signs is not always found. A fresh smear is recommended for the accurate diagnosis of infection. Erythrophagocytosis with infected erythrocytes may be found in blood smears from infected dogs. The use of molecular diagnostic assays such as PCR is indicative in cases of low parasitemia including suspected carrier dogs or chronically infected animals as well as for speciation.

Large *Babesia* spp. are treated with imidocarb dipropionate with good clinical response while small *Babesia* spp. appear to be more difficult to treat and resistant to the conventional drugs that are effective against the large babesial spp. (Table 2). Diminazene aceturate used for treatment of both large and small babesial spp. infections should be used cautiously as it has a relatively small dose safety margin with a large inter-individual pharmacokinetic variation. *Babesia gibsoni* infection is often resistant to imidocarb dipropionate and diminazene aceturate and its is mainly treated with the combination of the anti-malarial atovaquone and the macrolide azithromycin. However, complete clinical and parasitological cure are often not achieved in dogs treated for small babesial spp. infections and clinical relapses may occur. Medical management of infection may require supportive treatments including blood transfusions, intravenous fluids, and the use of anti-inflammatory drugs.

Table 2 - The main drugs used for treatment of canine babesiosis

Drug or combination	Dosage and route	References
Imidocarb dipropionate	6.6 mg/kg IM or SC; repeat dose in 2 weeks.	(Plumb, 2016)
Diminazene aceturate	3.5 mg/kg IM once	(Plumb, 2015)
Atovaquone + azithromycin	Atovaquone 13.3 mg/kg PO q8h and azithromycin 10 mg/kg PO once daily, both drugs for 10 days	(Plumb, 2015)
Buapravaquone + azithromycin	Buparvaquone 5 mg/kg IM twice 48h apart and azithromycin 10 mg/kg PO once daily for 10 days	(Checa et al., 2017)
Clindamycin + diminazene aceturate + imidocarb dipropionate (for atovaquone-resistant *Babes gibsoni*)	Clindamycin 30 mg/kg PO q12h; diminazene aceturate 3.5 mg/kg IM once on the day of treatment start; imidocarb diproprionate 6 mg/kg SC once on the day after diminazene is administered.	(Lin et al., 2012)