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CANINE BABESIOSIS

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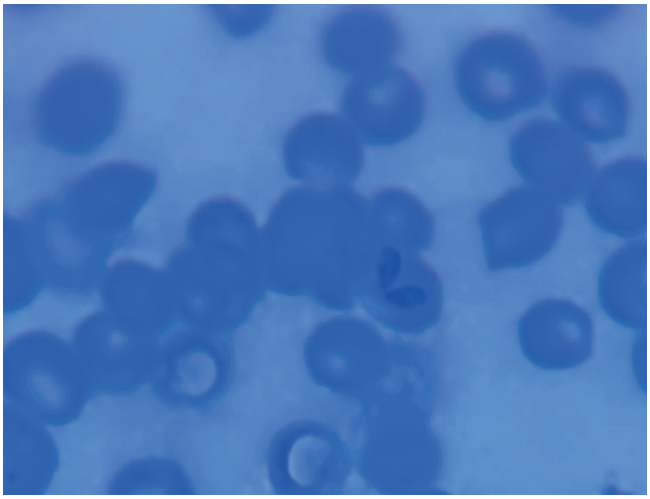


FIGURE 1:
Babesia sp – large form (B. vogeli) – blood smear from dog-ear tip showing merozoites
(light microscopy, 400x, oil immersion)
Source: Dr. Victor Ribeiro

Introduction:

Babesiosis is a major global disease caused by infection with intraerythrocytic protozoans of the genus Babesia (Figure 1), which causes hemolytic anemia, fever, and splenomegaly.

The disease can develop in several vertebrate species, including humans.

The infection ranges from asymptomatic to severe, developing into a life-threatening illness (Kuttler, 1988; Birkenheuer, 2012).

Species of ixodid ticks from several genera are the most common vectors of the pathogenic agent (Dantas - Torres & Figueiredo, 2006).

Synonyms:

Canine Piroplasmosis, spotted fever, “dog sadness” (apathy), tick-borne infection (Hipólito et al., 1965).

Classification:

The Genre Babesia belongs to the phylum Apicomplexa and contains more than 100 described species. However, this number may grow with current molecular biology analyses.

- Phylum: Apicomplexa
- Class: Aconoidasida
- Order: Pyroplasmida
- Family: Babesiidae
- Genera: Babesia
- (O'Dwyer & Massard, 2002)

Table 1: Historically, babesiosis-causing species have been identified according to their vertebrate host and size. Hence, based on its phenotype, Babesia is divided into two categories: large and small

Table 1: Babesia species, their geographical distribution, morphological characteristics, and identified vectors by groups of infected animals.			
Species	**Geographical distribution**	**Morphological characteristics**	**Vectors**
DOGS			
Babesia vogeli (B. canis vogeli).	Africa, Asia, North and South America, Europe and Australia	Large (2.4 x 4-7 µm) alone or in pairs, piriform-shaped	Rhipicephalus sanguineus sensu lato
B. canis (B. canis canis)	Europe	Large (2.4 x 4-7 µm) alone or in pairs, piriform-shaped	Dermacentor reticulatus, R. sanguineus sensu lato
B. rossi (B. canis rossi)	África	Large (2.4 x 4-7 µm) alone or in pairs, piriform-shaped	Haemphysalis elliptica, H. leachi
B. gibsoni	Africa, Asia, North and South America, Europe and Australia	Small (1-2 x 3-4 µm) mostly annular isolated bodies (ring-shaped)[1]	R. sanguineus sensu lato; H. bispinosa; H. longicornis
B. caballi (non-canine species)	Brazil (Pantanal)	Large (2-5 µm long) in pairs, piriform-shaped	Amblyomma sculptum; A. ovale; D. nitens
FELINES			
B. felis	Africa, South Asia, Europe	Small (0.9 x 0.7 µm), isolated or in pairs, ring-shaped	Ticks (undefined species)
B. cati	India	Small (1 x 1.5 µm), isolated or in pairs, ring-shaped	Ticks (undefined species)
B. leo	South Africa	Small x (1 x 1 µm), isolated or in pairs, round to oval-shaped	Ticks (undefined species)
B. microti-like spp (Theileria annae)	Portugal	Small to large (1 x 2.5 µm), isolated	Ticks (undefined species)

Species	Geographical distribution	Morphological characteristics	Vectors
B. canis presentii	Israel	Large (2.7 x 1.7 µm), single or paired, round to oval or ring-shaped	
B. herpailuri	Africa, South America	Large (1 x 2.5 µm), isolated or in pairs, ring-shaped	Ticks (undefined species)
B. panthera	Africa	Large (2.0 x 1.8 µm) shape not described	Ticks (undefined species)
B. canis canis	Spain, Portugal	Large (3 x 5 µm), single or in pairs, piriform-shaped	Ticks (undefined species)
Unidentified Babesia species related to Babesia spp in Japanese dogs	North America (Florida)	Not described	Ticks (undefined species)
HUMANS			
B. microti[2]	North America, Europe	Small, pleomorphic	Ixodes scapularis (Figure 1), I. trianguliceps, I. ricinus
B. divergens[3]	Europe	Small, pleomorphic	I. ricinus
B. divergens like	North America	Small, pleomorphic, high parasitemia	Unknown
B. venatorum (EU1)	Austria, Italy	Small, pleomorphic	Unknown
B. duncani	North America	Forming rings or tetrads	Unknown

[1] Some isolated B. gibsoni are large and have a heterogeneous appearance resembling B. canis. In this case, differentiation is only possible by molecular analyses (PCR).
[2].3 It is believed that humans are accidental hosts of Babesia species from animal reservoirs; some examples are B. microti (rodents) and B. diverge (cattle).
Source: Friedholff (1988), Ayoob (2010), Birkenheuer (2012), Baneth, 2018.

Canine disease:

The canine disease is distributed worldwide. The first descriptions of canine babesiosis occurred in Italy in 1895 (Hipólito et al., 1965) and Africa in 1896. The first case recorded in the USA took place in 1934 (Birkenheuer, 2012) while in 2005 in Brazil (Passos, 2005). Babesia vogeli was the first detected species in Brazil by Passos et al. (2005), conducting molecular analyses in dog samples from Minas Gerais and São Paulo States. Studies using molecular techniques enabled the identification of new species and genotypes year by year. In this way, B. canis, which was classified into three subspecies, is now considered as three distinct species (B. rossi, B. vogeli, B. canis), among even more newly described species (Table 1) (Irwin, 2009).

There is evidence for lack of cross-immunity between the different subspecies, and a serological cross-reaction can cause false-positive results for a species against which the patient has no protection (Soares, 2015).

Different Babesia species can cause similar diseases, but the transmission mechanisms and illness severity can vary greatly. The disease caused by B. rossi is considered the most pathogenic, followed by B. canis. Babesia vogeli and B. gibsoni are often described as mild or subclinically infectious in host animals (Table 2) (Birkenheuer, 2012; Soares, 2015). Babesia vogeli is the least virulent and, although it can cause clinical illness with severe anemia in puppies, it usually has low parasitemia in adult dogs, resulting in subclinical infections. This lack of virulence may be linked to a long association between B. vgoeli and domestic dogs (Köster et al., 2015). Thus, it is necessary to identify the species involved in each clinical case for better management (Birkenheuer, 2012).

Table 2: Babesia species according to their pathogenicity and geographical distribution

Species	Predominant geographical location	Pathogenicity
Babesia canis	Europe	The infection's clinical signs are highly variable, but typical signs are the onset of acute fever and hemolytic crisis. Some strains can cause severe babesiosis, such as in infections with B. rossi.

Species	Predominant geographical location	Pathogenicity
B. vogeli	Worldwide (Brazil)	It causes infections that are mostly asymptomatic or uncomplicated. Some dogs may have obvious clinical signs, while others may only exhibit fever of unknown origin, with no hematological changes.
B. rossi	South Africa	The range of clinical signs is highly variable. Most dogs have uncomplicated conditions and can be treated as outpatients. However, about 30% are hospitalized with serious conditions and, of these, about 10% die.
B. gibsoni	Worldwide (lower occurrence in Brazil)	Most dogs manifest uncomplicated conditions or are subclinical carriers.

Source: Birkenheuer, 2012; Daste et al., 2013; Soares, 2015.

Epidemiology

The epidemiology of babesiosis, including the canine version, is a complex and difficult subject because it is a vector-borne disease.

The relationships with their specific vectors establish the Babesia species distribution.

The international transport of dogs and cats increases the risk of transmission, exposes infected animals to new vectors that can become new sources of infection and transmission, and enables the possibility of developing new hosts (Birkenheuer, 2012).

The contact with new environments where the wild cycle between vectors and host naturally occurs leads to the detection of infections with new species of Babesia in humans and animals (Birkenheuer, 2012).

Around the world and distributed along their vectors, the most important species of canis, B. vogeli, B. rossi, and B. gibsoni (Soares, 2015) (Table 1).

FIGURE 2
Adult male of Rhipicephalus sanguineus
Source: https://www.cdc.gov/ticks/gallery/

In Brazil, B. vogeli (Figures 1 and 3) was recorded for the first time by Passos et al. (2005) and is widely disseminated throughout the national territory along its main vector, the tick Rhipicephalus sanguineus sensu lato (Figure 2). The Southeast and Northeast regions of Brazil stand out as the regions with the highest seroprevalence and infection rates (Maia et al., 2007; Soares, 2015; Barbosa et al., 2020). Maia et al. (2007) identified significantly higher seropositivity during April–June, reinforcing the idea that canine babesiosis is higher during the period of higher activity of vector ticks. A study by Vasconcelos (2010), using molecular techniques, on 187 Brazilian dogs from Brasília recorded B. vogeli in 43 (23%) and B. rossi in 5 (3%) animals. This report is the only one to inform the occurrence of B. rossi in Brazil, which is considered as confined to the sub-Saharan region, having the tick H. elliptica as its vector. Infection by B. gibsoni has also been detected in Brazilian dogs, but only by Trapp et al. (2006).

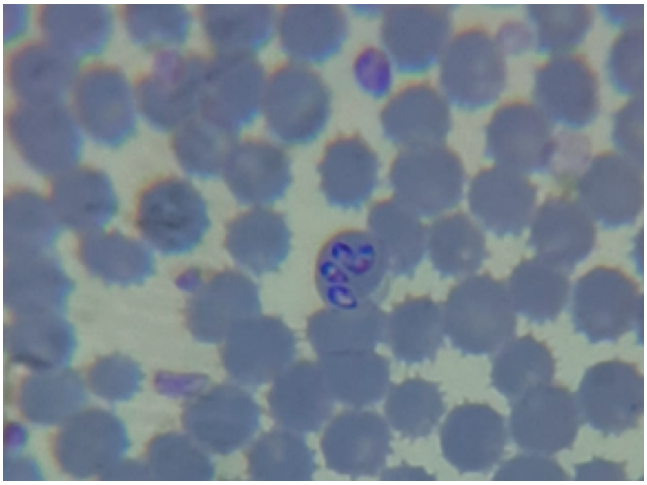
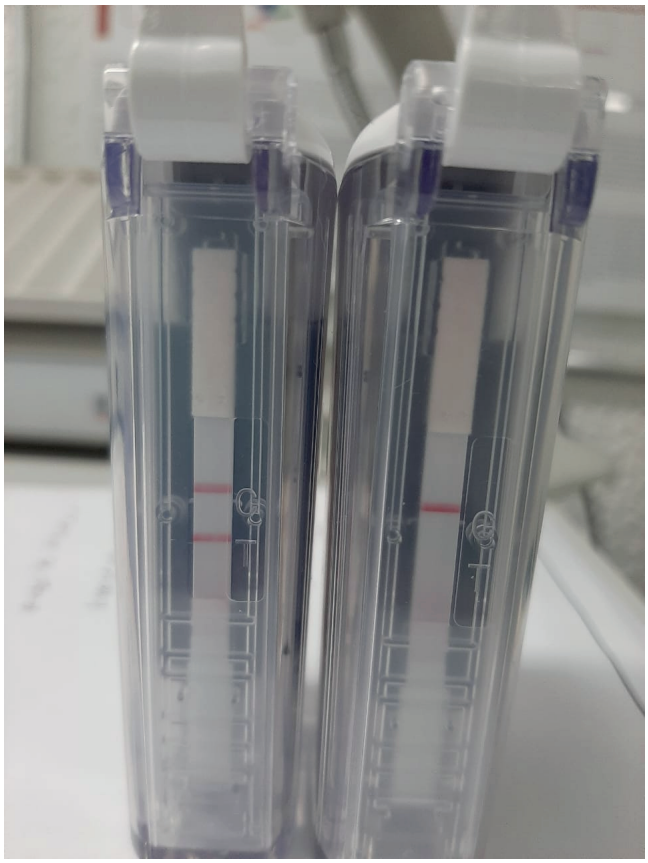


FIGURE 3:
A) blood smear from dog-ear tip showing merozoites (light microscopy, 400x, oil immersion)
Source: Dr. Victor Ribeiro



Babesia vogeli // Babesia gibsoni
B) PCRun Biogal® showing positive reaction for Babesia vogeli

Babesiosis affects young dogs, but they could be partially protected from a more aggressive condition, up to the age of 90 days, by maternal antibodies present in colostrum (Farwell et al., 1982).

Despite this protection, hyperacute conditions, including neurological signs, have been described in dogs less than four weeks old (Abdullahi et al., 1990).

The acute form, with more severe cases, has been reported in dogs between three–six months (Ribeiro et al., 1990) to one year of age (Abdullahi et al., 1990; Breitschwerdt et al., 1983; Lobetti, 1995; Solano-Gallego & Baneth, 2011; Birkenheuer, 2012). In adult dogs, the condition tends to be mild, and asymptomatic infections can last for up to 95 days (Wang et al., 2018).

A study by Wang et al. (2018) showed that dogs experimentally infected at seven–eight months of age with B. vogeli developed mild clinical signs followed by asymptomatic infections that lasted for at least 95 days. However, the authors found that the disease manifestation in splenectomized dogs was severe and included the risk of death (Wang et al., 2018). These chronic infections associated with B. vogeli and B. gibsoni are epidemiologically important because of the wide local distribution of seroprevalence and infection.

Biological cycle

Modes of transmission – bite from the infected vector (it is the natural and most frequent way of transmission) (Dantas-Torres & Figueiredo, 2006). Other unusual forms of transmission described are blood transfusion with infected donors, transplacentally transmission, physical contact, wounds from dog fights, saliva, and blood ingestion (Birkenheuer et al., 2005; Jefferies et al., 2007; Yeagley et al., 2009; Birkenheuer, 2012; Solano-Gallego et al., 2016).

Life cycle – Infected ticks inoculate the infective forms (sporozoites) while blood-feeding, through their saliva, to susceptible animals.

A study showed that the male tick Dermacentor reticulatus transmitted B. canis to dogs eight hours after adherence (Varloud et al., 2018). However, Leisewitz (2020) and Irwin (2020) stated that a tick adhesion greater than 24 hours and between 48-72 hours is necessary for transmission to occur.

Sporozoites in the bloodstream bind to erythrocytes and undergo endocytosis. Inside the red blood cells, sporozoites acquire a rounded shape becoming trophozoites. Trophozoites evolve into merozoites that initiate asexual reproduction (merogony) by binary fission. After successive merogonies, the red blood cells rupture and free merozoites that go on to infect new erythrocytes (Birkenheuer, 2012; Soares, 2015). Some merozoites within red blood cells differentiate into gametocytes or undergo this differentiation already in the tick intestine (Soares, 2015).

An uninfected tick ingests erythrocytes infected by merozoites or gametocytes precursors. In the midgut of the tick, the sexual reproduction of the Babesia is complete when female and male gametocytes fuse to form an ookinete zygote. The zygote invades the tick's gut epithelial cell, and an asexual form of reproduction (sporogony) then results in sporozoites production. These sporozoites break down intestinal cells, invade new tick cells, and undergo new sporogony. This infection takes over the salivary glands and ovaries of the tick, leading to transstadial, and transovarial transmissions, respectively (O'Dwyer & Massard, 2002; Birkenheuer, 2012; Soares, 2015, Jongejan et al., 2018). In this way, ticks will transmit the infective forms to dogs from different stages, such as larva, nymph, and adults..

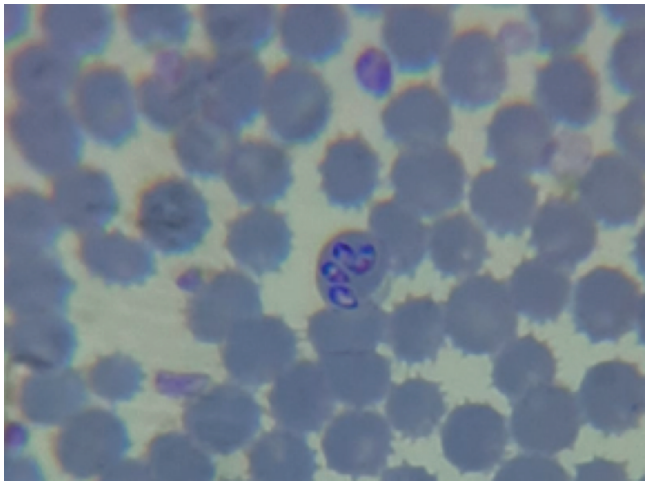
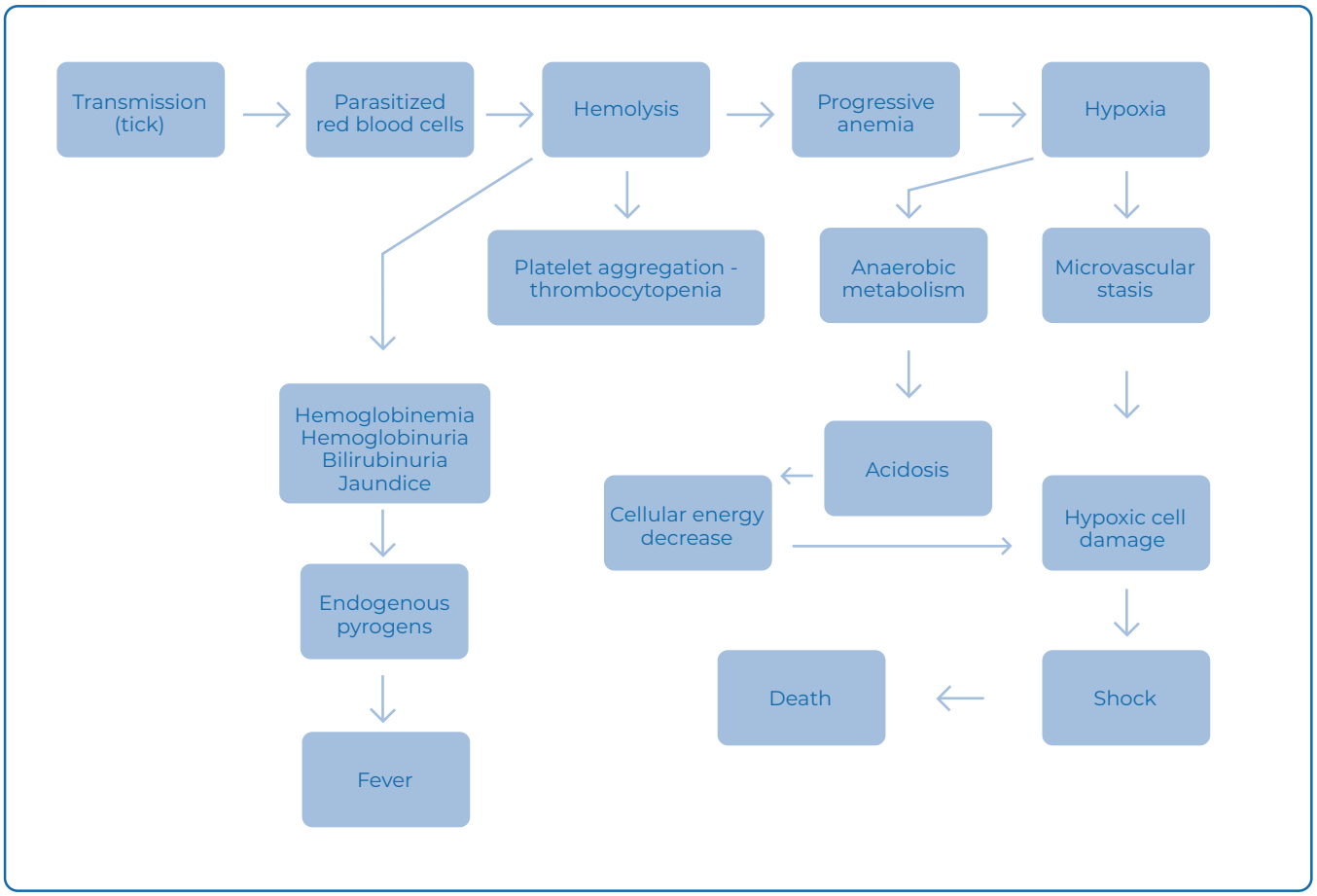


FIGURE 4:
Pathogenesis of canine babesiosis



Pathogenesis (Figure 4):

Is associated with the hemolytic action of the parasite, and its intensity is primarily determined by the species and strains involved (O'Dwyer & Massard, 2002; Birkenheuer, 2012). There is a hemolytic process through both the reproduction and activity of the parasite inside the red blood cells leading to their rupture and erythrophagocytosis by the mononuclear phagocytic system (MPS), as a consequence of the parasite's antigens exposed on the surface of red blood cells and the weakening of the membranes exposing the red - cell antigens (Soares, 2015).

In addition, soluble parasite antigens can adhere to the surface of uninfected erythrocytes and platelets, leading to the opsonization of these cells by antibodies and their removal by the MPS.

This phenomenon can occur independently of the parasitemia level (Birkenheuer, 2012).

Furthermore, the exposure of erythrocyte antigens can lead the host to develop anti-red cell membrane antibodies, increasing macrophage activity, contributing to the evolution of babesiosis - associated immune - mediated hemolytic anemia (IMHA) - (Birkenheuer, 2012).

He hemolysis process leads to regenerative anemia, with reticulocytosis and nucleated red blood cells (O'Dwyer & Massard, 2002). With increased lysis of red blood cells, the ill animal manifests hemoglobinemia, hemoglobinuria, and bilirubinemia and develops a typical pre-hepatic jaundice process (Leisewitz, 2020). In addition, red blood cell lysis also leads to the release of pyrogens with an elevation of body temperature (Soares, 2015; Leisewitz, 2020), an influx of neutrophils, and exacerbatiotn of the inflammatory process.

The formation of parasitized red cell clusters due to vascular stasis in capillary networks contributes to the acute anemic process, among many other clinical signs. The most severe agglomeration occurs in the central nervous system (CNS) and muscles (Birken-heuer, 2012).

Splenomegaly and hepatomegaly are signs of congestion of these organs and MPS hyperplasia (Soares, 2015).

Thrombocytopenia alone or together with other changes can be observed in many cases associated with an immune-mediated process of platelets coagulation due to vascular injury or hemolytic conditions (Birkenheuer, 2012; Irwin, 2020).

Disseminated intravascular coagulation can be a devastating complication (Birkenheuer, 2012). Despite this decrease in platelet count, bleeding processes are rare and, in more severe cases, associated with B. rossi.

Anemia produces tissue hypoxia that increases anaerobic metabolism, leading to metabolic acidosis that is an important factor in many of the clinical signs caused by the more pathogenic strains of Babesia (Birkenheuer, 2012; Soares, 2015). The generation of lactic acid due to tissue hypoxia is the main cause of metabolic acidosis (Birkenheuer, 2012).

Other causes of tissue hypoxia in dogs infected with Babesia are anemia, shock, vascular stasis, excessive production of endogenous carbon monoxide, parasitic hemoglobin damage, and decreased ability of hemoglobin to release oxygen. Hypoxia appears to be more important than hemoglobinuria in kidney damage.

Glomerulonephritis can be explained by two mechanisms: severe hemolytic anemia leading to potential tubular damage, interstitial nephritis, and glomerulopathy; and the immune-mediated mechanism resulting from the deposition of immune complexes in the glomeruli. These two processes can also occur in the CNS (Cavalcante et al., 2006; Daste et al., 2013).

Atypical changes can occur in dogs affected by more pathogenic strains of Babesia. Most notably, B. canis and B. rossi can induce a profound systemic inflammatory response.

A syndrome similar to septic shock has been described in some dogs infected with large forms of Babesia. Tissue damage from infection likely causes the release of cytokines, leading to inflammation and additional damage to multiple organs. Multiple organ dysfunction syndrome leads to systemic inflammatory response syndrome (SIRS), including acute renal failure, liver disease, immune - mediated hemolysis, pulmonary edema, rhabdomyolysis, and brain dysfunction. Injuries in lungs, CNS, and renal complications are associated with a high mortality rate. These manifestations are rare in infections with B. gibsoni and B. vogeli (Brandão & Hagiwara, 2002; Birkenheuer, 2012).

Clinical signs

Clinical signs vary according to the Babesia species involved, and even infections by less pathogenic species such as B. vogeli may have a severe clinical manifestation in some animals and even lead to death (Vince, 2016). However, other animals may be asymptomatic, without laboratory test alterations, even when infected by the "virulent" B. rossi (Birkenheuer, 2012).

The incubation period is about 10–28 days, which means that the disease manifests itself after the tick vector has fed and shed its host, a process that is usually completed within a week (Köster et al., 2015).

The severity of clinical signs can be associated with factors such as the pathogenicity of the strain of Babesia involved, parasitemia intensity, immune response, age of the host, and concomitant infections (Martinod et al., 1986; Soares, 2015).

Regarding clinical signs, we can classify the infection as subclinical (unapparent), acute and hyperacute, or as uncomplicated or complicated (O'Dwyer et al., 2002; Birkenheuer, 2012).

Many dogs that become infected and show mild signs such as apathy and fever can spontaneously recover and become asymptomatic carriers. However, in situations of intense stress and/or concomitant infections, the same dogs can get sick again (O'Dwyer et al., 2002).

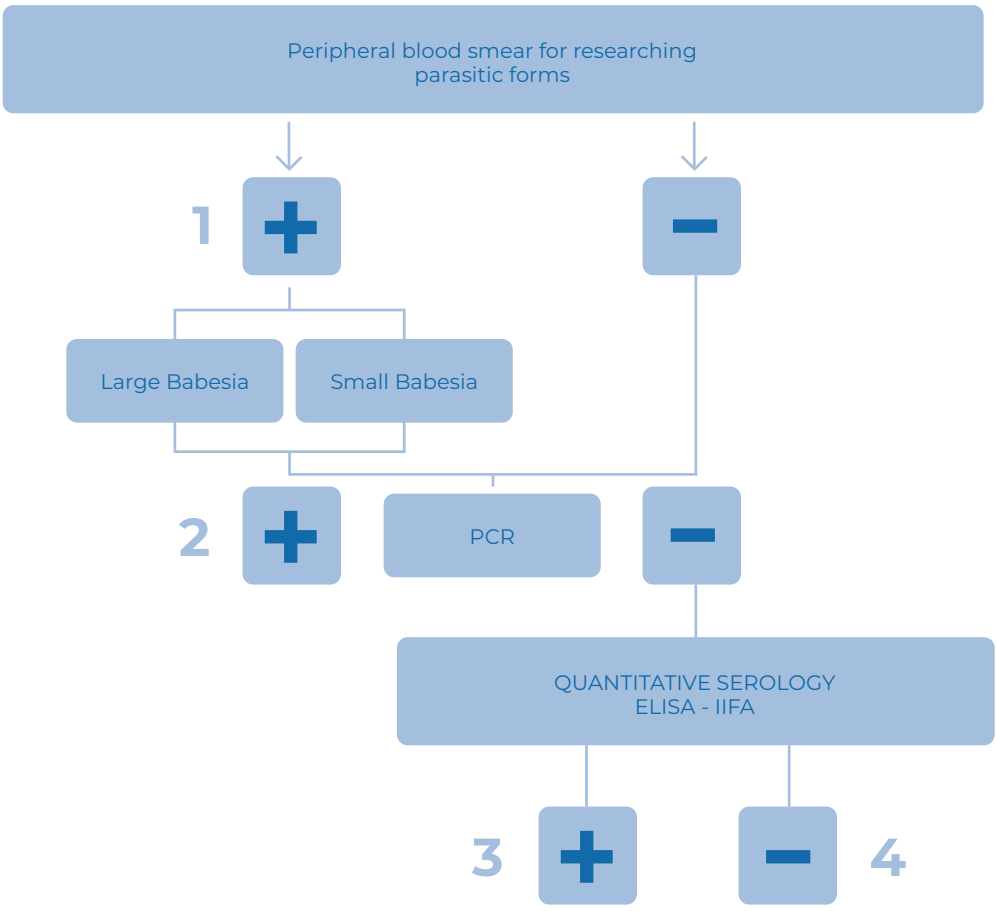
The most common clinical signs indicating infection with Babesia and classification of disease manifestation are listed in **Table 3.**

Table 3: Clinical signs and classification of babesiosis manifestation in dogs

Clinical signs	Classification - manifestation
USUAL:	HYPERACUTE (complicated):
Mild to severe anemia Fever (hyperthermia) Apathy Anorexia Lethargy Weakness Loss weight Lymphadenopathy Splenomegaly Hepatomegaly	Intense anemia Hypothermia Shock Coma Disseminated intravascular coagulation Metabolic acidosis Acute kidney failure Acute pancreatitis CNS signs (seizures) Death
UNUSUAL (most associated with B. rossi):	ACUTE (uncomplicated):
Shock Neurological manifestations (seizures, ataxia, paresis) Respiratory disorders Bleeding (petechial/suffusion) Coagulation disorders Ascites Edema Diarrhea Constipation Ulcerative stomatitis Polycythemia Nasal and ocular discharge Myositis of masticatory muscles Temporomandibular pain	Hemolytic anemias Jaundice Splenomegaly Lymphadenomegaly Vomiting Change in urine color (bilirubinuria/hemoglobinuria)
	INAPPARENT (subclinical):
	* Asymptomatic * Soft signs: - Fever - Apathy - Mild anemia - Anorexia Dogs tend to spontaneous recover and become carriers

Source: Adapted from O'Dwyer et al., 2002; Birkenheuer, 2012; Soares, 2015.°

Dogs with clinical signs and clinicopathological alterations compatible with babesiosis



CAPTION:

1 – Distinguishing between Large and Small Babesia helps in the immediate onset of treatment.

2 – Molecular techniques contribute to species identification – Babesia canis; B. vogeli; B. Rossi; B. gibsoni.

3 – Indicates exposure, but neither identifies species nor confirms infection. Repeat after 2-3 weeks to assess titer growth.

4 – Repeat every 4-8 weeks to assess seroconversion and searching for other infections.

Diagnosis:

From a clinical point of view, we may suspect a case of babesiosis in dogs that have a history of tick infections, especially when young, and that are febrile, apathetic, and anorectic, with pale mucous membranes and jaundice (O'Dwyer et al., 2002; Birkenheuer, 2012; Soares, 2015).

These signs, although suggestive, must be followed by laboratory tests to confirm the infection (Figure 5) and identify the infection stage through clinical pathology tests (blood count, biochemical tests, urinalysis) (O'Dwyer et al., 2002; Irwin, 2020

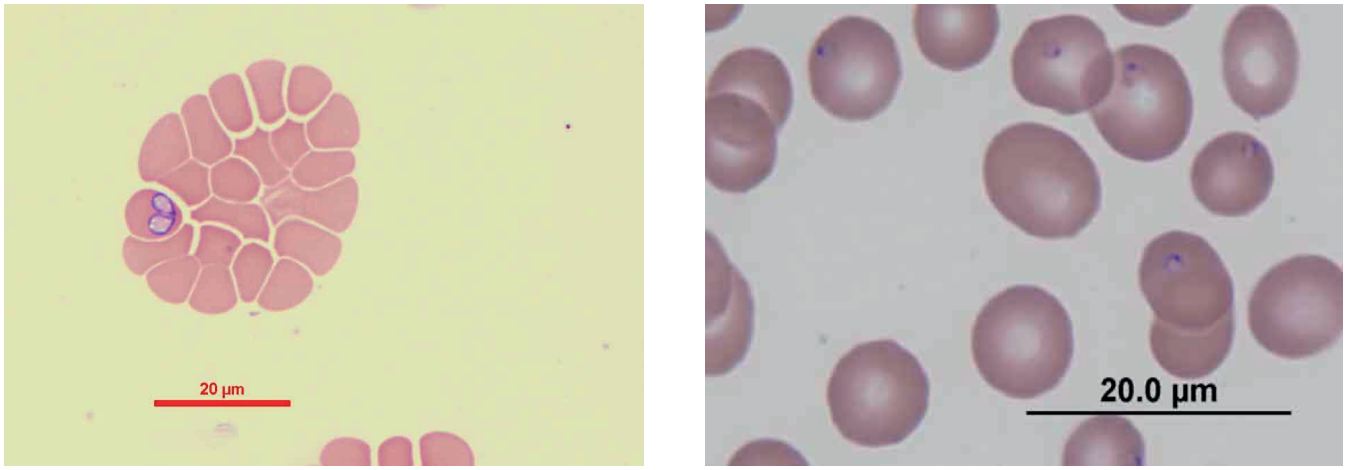


FIGURE 6:
A) Babesia vogeli inside an erythrocyte.
B) Babesia gibsoni inside erythrocytes
Images Dr. P. Irwin, available
at: https://www.troccap.com/canine-guidelines/other-systems/babesia/

Parasitological/molecular diagnosis:

Parasitemia is higher in the acute phase, making the parasites more frequently observable in peripheral blood smears (Figures 1, 3A, 6A-B) (Kidd, 2019). The blood should be collected from peripheral capillaries, mainly from the tip of the ears (O'Dwyer et al., 2002) or tail (Soares, 2015).

This method is considered to have low).

sensitivity and is not recommended as a sole diagnostic test.

Furthermore, blood examination under light microscopy cannot be used to distinguish between different Babesia species. However, microscopy visualization of the parasitic forms (merozoites), associated with anamnesis, physical aspects,

and laboratory tests, can help the clinician determine the most likely species (Birkenheuer, 2012).

Considering morphology, B. canis, B. vogeli, and B. rossi are typically large, piriform - shaped, and usually seen singly or in pairs (Figure 6A), while small, isolated, and annular forms are probably associated with B. gibsoni (Figure 6B) (Lapin, 2010; Birkenheuer, 2012; Soares, 2015).

Molecular techniques, unlike direct detection by light microscopy or antibody detection by serology, allow more reliable identification of dog - infecting species (Figure 3B) (Solano - Gallego & Baneth, 2011; Birkenheuer, 2012). Even though considering the lower detection limit of some PCR assays, they still are 1300 times more sensitive than light microscopy at detecting the infection in parasitized erythrocytes that are about 0.001% of the red cells (Birkenheuer, 2012). There are various PCR techniques available on the market, and those that can differentiate the species involved are more suitable for deciding between the different treatments required (Lappin, 2010; Birkenheuer, 2012; Baneth, 2018; Irwin, 2020). Multiplex PCR, which seeks to detect several vector - transmitted agents, has shown benefits for detecting coinfections, especially ones involving E. canis and A. platys (Birkenheuer, 2012; Irwin, 2020). Another advance linked to molecular examination is a technique called PCRun. This technique has advantages over standard PCR due to its simplicity and speed, as it can be completed within 75 minutes.

It can be performed in the hospital, clinic, or laboratory environment and has high sensitivity and specificity for identifying different Babesia species (https://www.biogal.com/products/pcrun-detection-kit/technical-information/).

Serological diagnosis

In most animals, seroconversion begins occurring on the seventh day after infection. Thus, serological tests are not suitable for recent infections (Soares, 2015) as they can result in false negatives for both young and adult dogs (Birkenheuer, 2012; Kidd, 2019). The techniques used for these tests are the indirect immunofluorescence assays (IFA) and the enzyme - linked immunosorbent assays (ELISA) (Ramsey et al., 2001; Soares, 2015).

It is not useful to perform these tests during acute infection or to use them to differentiate between Babesia species due to extensive cross - reaction. False-negative results may occur if the onset of an acute illness precedes the development of antibodies. However, serological detection of anti - Babesia antibodies suggests previous exposure or chronic infection, making these tests useful in epidemiological surveys (Soares, 2015).

Furthermore, serological testing can be very useful for diagnosing subacute or chronic forms of infection in which the parasites are present in low numbers or absent in the blood (Kidd, 2019). However, many seropositive dogs are clinically normal. In such cases, serology should not be used alone to identify the infection or decide on treatment (Lapin, 2010).

Preferably, serologic tests should be used in paired serum samples taken two or three weeks apart to assess whether antibody titer elevations are consistent with recent infection or active babesiosis (Lapin, 2010).

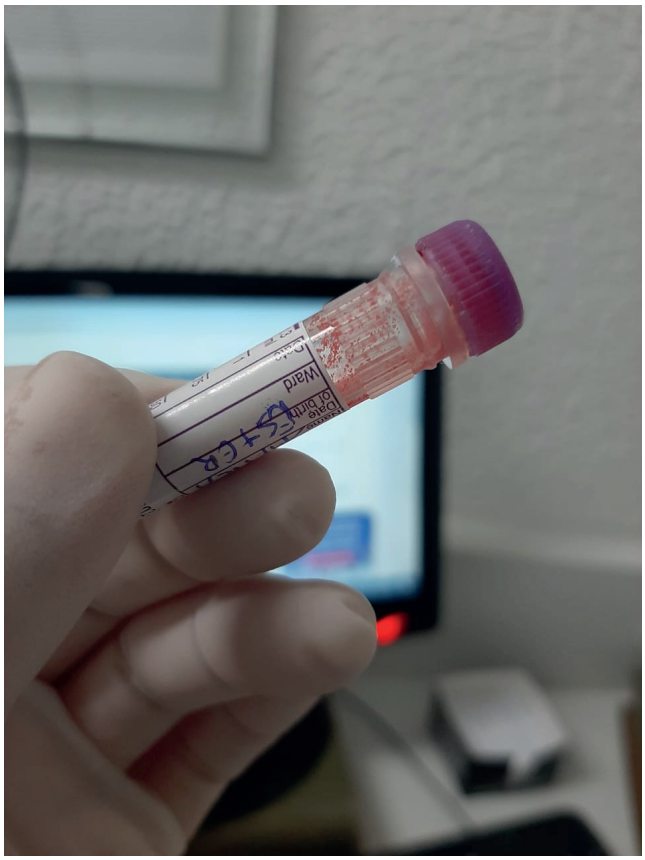


FIGURE 7:
Occurrence of agglutination in a blood collection tube
Source: Dr. Victor Ribeiro

Clinical pathology and immunological tests:

* Complete blood count – anemia with reticulocytosis (regenerative), anisocytosis, polychromasia, neutrophilic leukocytosis, thrombocytopenia, and giant platelets:

  - In the first days after infection, anemia tends to be mild, normocytic, and normochromic, though it can become macrocytic, hypochromic, and regenerative with the evolution of the disease.

  - Reticulocytosis is proportional to the severity of the anemia.

  - The leukocyte count varies and may go from leukocytosis to leukopenia. In our experience, however, leukocytosis with neutrophilia is more frequent and may be related to the acute phase of the disease.

  - Immune-mediated hemolytic anemia (IMHA) can be evaluated using the tube agglutination test and the Coombs test (Figure 7) and should precede blood transfusions that are sometimes necessary.

* Biochemistry – hyperbilirubinemia, hyperglobulinemia, hypoalbuminemia, hemoglobinemia, elevated liver enzymes (ALT, AST, FA), serum levels of urea and creatinine, hypokalemia, hyponatremia, hypochloremia, hyperlactatemia, and hypoglycemia.

  - Urinalysis – bilirubinuria, hemoglobinuria, and proteinuria.

(Brandão & Hagiwara, 2002; O'Dwyer et al., 2002; Lappin, 2010; Birkenheuer, 2012; Thrall, 2015; Sharma et al., 2016; Irwin, 2020).

Treatment:

Treatment is sometimes established on the basis of clinical, epidemiological, and therapeutic response criteria (Soares, 2015).

Another important condition to be considered when choosing the treatment refers to the Babesia species involved since treatment against B. gibsoni differs from treatment against B. vogeli (Table 4) (Lappin, 2010; Lin et al., 2012; Baneth, 2018).

Supportive therapy

* Blood transfusion
* Fluid therapy
* Treatment of comorbidities (Ehrlichia canis, Leishmania infantum, Rangelia vitalli, among others).

Specific treatment

Treatments for the disease and control of the parasite load, or elimination of the parasite, are presented in **Table 4**. Note that the drugs and treatments used vary depending on the species involved.

Table 4: Main drugs used alone or combined to treat canine babesiosis according to the species involved

Species	Single drug or drugs combination	Dosing	Comments
Babesia canis / B. vogeli / B. rossi	Imidocarb dipropionate	5-7 mg/kg IM, SC - repeat after two weeks	Injection site pain or injection site lump / cholinergic signs (vomiting, salivation, diarrhea) can be managed with atropine (0.05 mg/kg sc)*
	Diminazene aceturate	3.5 mg/kg IM single application	Gastrointestinal disorders include vomiting and diarrhea, pain and inflammation at the injection site, transient drop in blood pressure, and, more rarely, neurological signs, including ataxia, seizures, and death. Atropine (0.05 mg/kg SC) can also be applied against signs of intoxication*
B. rossi	Trypan blue	10 mg/kg single dose	Tissue irritant (use 1% solution). Reversible staining of tissues
	Phenamidine isethionate	15 mg/kg IM, repeat after 24 hours	Nausea, vomiting, and CNS signs
	Pentamidine isethionate	16.5 mg/kg IM, repeat after 24 hours	

Species	Single drug or drugs combination	Dosing	Comments
B. gibsoni	Atovaquone + azithromycin	13.3 mg/kg orally, every 8 hours + 10 mg/kg orally once a day (both for 10 days)	Currently, there are no known adverse effects of atovaquone in dogs.* Combining clindamycin, imidocarb, and diminazene showed an advantage over treatments with atovaquone and azithromycin (Lin et al., 2012).
	Bupavaquone + azithromycin	5 mg/kg IM, every 48 hours + azithromycin 10 mg/kg orally, once a day for 10 days	
	Clindamycin + diminazene + imidocarb (for atovaquone resistant B. gibsoni)	30 mg/kg orally, every 12 hours + 3.5 mg/kg IM, on the first day of treatment + 6 mg/kg SC, once a day after application of diminazene	

Source: adapted from Solano-Gallego et al., 2016; Baneth, 2018; Irwin, 2020.
*Viana, 2019.

It has been considered unlikely that treatment will always eliminate the carrier status (Lappin, 2010; Thrall, 2015). As there are no medications available that consistently eliminate infections by different Babesia species, the treatment of healthy seropositive dogs should be analyzed as it may not be beneficial. For those in whom the infection is identified by PCR or blood smears, the stage of the disease should be analyzed before treatment (Lappin, 2010), except for those animals presenting coinfections, such as by L. infantum. Another condition that should be pointed out is the non-use of these dogs as blood donors (Table 6).

Control:

Prevention of piroplasmosis requires dogs to be kept free from exposure to ticks, avoid fighting with other dogs, and careful examination of any blood transfusions to ensure absence of the parasite (Irwin, 2010).

For tick control, the products most locally used on dogs are listed in Table 5.

Table 5: Tick Control per Products			
Products	**Adhesion prevention**	**Age (weeks)**	**Interval**
Fipronil	No	≥ 8 weeks	Monthly
Topical Permethrins Deltamethrin Cypermethrin Alphamethrin Flumethrin	Yes	≥ 8 weeks	Monthly
Collars Deltamethrin 4% Permethrin 4% Flumethrin 4.5% Amitraz	 Yes Yes Yes Yes	 ≥ 12 weeks ≥ 40 weeks ≥ Seven weeks ≥ 12 weeks	 4 months 8 months 8 months 2-3 months
Amitraz	Yes	> 8 weeks	Monthly
Chewable tablets (Isoxazolines) Sarolaner Afoxolaner Lotilaner Fluralaner	 No No No No		 Monthly Monthly Monthly 12 weeks (8 weeks for Amblyomma)

Source: adapted from Littman et al., 2018.

Specific treatment

A strict dog donor program must be implemented, as shown below in **Table 6.**

Table 6: Recommendations for screening canine blood donors for bloodborne pathogens (Wardrop et al., 2016)

Agent	Ideal standards	Minimum standards	Comments
Babesia canis vogeli	Seronegative and PCR negative, especially in high-risk dogs.	PCR negative	High-risk dogs include greyhounds and those with a history of exposure to Rhipicephalus ticks.
B. gibsoni	Seronegative and PCR negative, especially in high-risk dogs.	PCR negative	High-risk dogs include pitbull terriers and those with a history of aggressive interactions with pitbull terriers.

Source: adapted from Wardrop et al., 2016.

Control:

There has been a significant increase in the amount of information about canine babesiosis available in Brazil, but there are still gaps in diagnosis, treatment, and prevention.
Veterinarians must be aware of the possible species that can infect dogs in Brazil and the decision of whether to treat seropositive and even infected animals, depending on the stage of the infection. Another aspect that needs to be understood involves coinfection or positive serology in dogs infected with Leishmania.

This review aimed to provide additional information to better understand both this infection and the importance and frequency of existing coinfections. Fast diagnosis with correct handling and treatment will ensure the health of our patients..

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