Chapter

Overview of Canine Babesiosis

Poonam Vishwakarma and M.K. Nandini

Abstract

Canine babesiosis is a tick-borne, protozoal, haemoparasitic disease that can cause varying degrees of haemolytic anaemia, splenomegaly, thrombocytopenia and fever. There are two hosts for the transmission of *Babesia* spp., viz. invertebrate (tick) and vertebrate host. Dogs are one among the many targets of *Babesia* spp., causing canine babesiosis, and now there are clinical evidences of possible vertical transmission too. Dogs of all ages can be affected with *Babesia* spp., but young puppies are more commonly affected. Considering advanced diagnostic techniques, for an early and specific detection of acute infections, an AgELISA that is potentially translatable to a rapid diagnostic test design is reported. Different molecular techniques used for identification and differentiation of the various species of Babesia are semi-nested PCR, reverse line blotting and PCR-restriction fragment length polymorphism analysis. Treatment consists of three components: treatment with antiprotozoal agents to eliminate the parasite, blood transfusions to treat severe anaemia and supportive care for the complications and metabolic derangements. Blood lactate concentrations can serve as a prognostic indicator in severe or complicated canine babesiosis. For prevention apart from conventional measures, vaccines against *Babesia* species such as *B. gibsoni* are currently being developed.

Keywords: haemolytic anaemia, babesiosis, reverse line blotting, intraerythrocytic, blood lactate, semi-nested PCR

1. Introduction

Canine babesiosis is a clinically significant tick-borne disease caused by apicomplexan parasites of the genus *Babesia* which has been reported worldwide including India. These verity of the disease depends on multiple factors such as the type of *Babesia* species involved, the age and the immune status of the host [1, 2]. It is caused by different *Babesia* species with a worldwide distribution characterised by erythrocyte destruction causing mild to severe systemic clinical manifestations [3] like varying degrees of haemolytic anaemia, splenomegaly, thrombocytopenia and fever.

2. Classification

Babesia organisms are frequently classified as large or small. Historically, *Babesia* spp. in dogs was identified by their morphological appearance in erythrocytes of blood smears (intraerythrocytic merozoite stage). Initially, all large forms measuring between 3 and 5 μm were classified as *B. canis*, whereas all small forms measuring 1–3 μm were designated as *B. gibsoni*, but molecular analysis and DNA

sequencing have revealed that there are at least three small piroplasms infecting dogs, viz. *B. gibsoni*, *B. conradae* and the recently reported "*Babesia vulpes*" [4].

In former times, on the basis of cross immunity, serological testing, vector specificity and molecular phylogeny, *Babesia canis was* categorised into three subspecies (*B. canis canis*, *B. canis rossi*, *B. canis vogeli*) [5, 6], but now these subspecies are considered as separate species [7, 8].

3. Prevalence

Out of three previously considered subspecies, *Babesia rossi* is the most virulent species and occurs predominantly in southern Africa. *Babesia vogeli* is the least pathogenic species occurring in France, Australia, Japan, Brazil, South Africa and the USA and usually causes mild disease in adult dogs but severe disease in some puppies [9]. *Babesia canis* is of intermediate pathogenicity and is widespread in Europe and Asia.

B. gibsoni, the smaller piroplasm is prevalent mainly in the Middle East, southern Asia, Japan, North Africa and South America and is an emerging infectious disease in the USA, as well as having been detected lately in Italy, Hungary and Australia [10]. A more virulent subspecies of *B. gibsoni* has also been identified in California [11]. *Babesia microti*-like piroplasma, *B. annae* (also known as *Theileria annae*), has been found to be endemic in dogs in northwest Spain [12]. In India both *B. canis* [13, 14] and *B. gibsoni* [15, 16] are prevalent, and almost all states of the country are affected.

4. Zoonotic importance

Babesia species affecting dogs and/or cats are not reported to be of zoonotic importance [17]. However, dogs and cats are close companions of people and can serve as a source of infected ticks for humans [18]. Human babesiosis is a rare disease and primarily involves just two species of *Babesia*: *Babesia divergens*, a parasite of cattle in Europe, and *Babesia microti* that parasitizes small rodents in the USA.

5. Transmission

There are two hosts for transmission of *Babesia* spp., viz., invertebrate (tick) and vertebrate host. Dogs are one among the many targets of *Babesia* spp., causing canine babesiosis (formerly called canine piroplasmosis).

Hard ticks are the main vectors for *Babesia* spp. Species such as *Rhipicephalus sanguineus*, *Dermacentor* spp. and *Haemaphysalis ellipticum* can transmit the large *Babesia* of dogs, whereas *B. gibsoni* is transmitted by *Haemaphysalis bispinosa* and *Haemaphysalis longicornis*. *Babesia annae* is thought to be transmitted by *Ixodes hexagonus* [19]. Both trans-stadial and transovarial transmissions can occur, and ticks are believed to remain infective for several generations.

Babesia spp. undergoes the sexual conjugation and the sporogony portions of their life cycles inside the lumen of the intestine and then within the haemocoel of the tick. Then the sporozoites from the tick's salivary gland are transmitted to their new vertebrate host via a blood meal, and thereafter the protozoan life cycle is completed within the red blood cells by asexual replication (merogony), where the parasites appear as merozoites [20], which leaves the host cell and enters another red blood cell. This cycle continues for the entire life tenure of vertebrate host or

until the host's immune system terminates the process. However, in many countries for the last one decade, *Babesia gibsoni* infections have been reported in the absence of tick vectors. There is now convincing evidence that these cases have arisen due to biting and fighting between infected and noninfected dogs [21, 22], but these parasites are primarily transmitted through tick bites. This association arose as a by-product of the tick's adaptation to feed on blood.

The first clinical evidence of possible vertical transmission has been documented for *B. canis* [23] and *B. microti*-like spp. [24]. Although *Babesia* undergoes part of their life cycles in ticks, the merozoites circulating in the blood may be transmitted to a healthy host directly by blood transfusion. This scenario has been described for *B. gibsoni* infection [25] and by direct contact between dogs through wounds (fighting dogs), saliva or blood ingestion [21, 22, 26].

6. Clinical signs and pathogenesis

Dogs of all ages can be affected with *Babesia* spp., but young puppies are more commonly affected. The incubation period varies from 10 to 21 days for *B. canis* and 14–28 days for *B. gibsoni*. Mortality for *Babesia* spp. infections ranges from 12% for *B. rossi* to approximately 1% for *B. vogeli* [19].

The most predominant feature of babesiosis in infected dogs are haemolytic anaemia and thrombocytopenia. Multiple causes like extra- and intravascular haemolysis, RBC destruction due to increased osmotic fragility, shortened life span of RBCs, erythrophagocytosis and immune-mediated destruction of RBCs because of parasitic antigens, parasite-induced membrane damage and possibly other membrane-associated antigens leads to anaemia [27–29]. Impaired haemoglobin function, oxidative damage, sludging and sequestration of erythrocytes also likely occur [27, 28, 30].

Recent study revealed about the renal involvement in babesiosis. Hypoxaemia, glomerulonephritis and haemoglobinuric nephropathy are considered possible mechanisms and supported by histological studies [31].

Pancreatitis is frequently associated with other complications and has a mortality rate of 20%. Common finding includes vomition, melaena, icterus, abdominal pain and diarrhoea. In addition, 65% of the dogs with pancreatitis also had icterus, 30% had acute respiratory distress syndrome (ARDS), 30% had immune-mediated red blood cell destruction (IMHA), and 15% had acute renal failure (ARF), while 10% had haemoconcentration, and another 10% had cerebral syndrome. It is postulated that pancreatitis is formerly described "gut" form of babesiosis [32].

The severe form of disease is characterised by marked haemolytic anaemia and acid–base abnormalities [33] with secondary multiple organ failure and complications such as ARF, hepatopathy, hypoglycaemia [34], ARDS, IMHA and cerebral pathology [35]. Small subset of dogs presents with high haematocrits (relative haemoconcentration), despite vigorous haemolysis, due to shifting of fluid from intravascular to extravascular component. These dogs are at increased risk of developing ARF or cerebral complications, as well as other organ failures [36].

The severity of the disease depends on the species of *Babesia*, presence of concurrent infections, age and immune status of the host. The disease presentation varies widely from peracute to chronic or even subclinical. *Babesia rossi*, the dominant species found in South Africa, is very virulent and causes peracute and acute disease. Most common signs include fever, anorexia, weakness, depression, pale mucous membranes, tachycardia, tachypnoea and splenomegaly. Clinical signs are because of tissue hypoxia following anaemia and a concomitant systemic inflammatory response syndrome caused by marked cytokine release [19].

Babesia vogeli causes clinically inapparent infection in mature dogs. The parasitaemia is very low, and infection may be missed while routine examination of blood smear. Subclinical infections are common in adult dogs, but puppies tend to present with marked anaemia [37]. It is endemic in greyhound kennels in the USA, and particular care should be taken when relocating greyhounds that can harbour subclinical infections.

Babesia canis infections result in a more variable pathogenicity, intermediate between *B. rossi* and *B.vogeli*. Anaemia is reported in majority of dogs and thrombocytopenia in all cases [38].

Babesia gibsoni infection follows either hyperacute, acute or chronic course. Among these acute course is the most common and is characterised by fever, lethargy, haemolytic anaemia, thrombocytopenia, lymphadenopathy and splenomegaly [39]. The hyperacute state is rare and is characterised by shock and extensive tissue damage. Mostly a disease of American Pit Bull and Staffordshire Bull Terriers is transmitted via dog bites [21]. In Australia and the USA, subclinical *B. gibsoni* infections have been reported, where they are PCR positive, but neither show clinical illness nor microscopic parasitaemia [40]. Such cases can have dire consequences if imported into non-endemic areas.

Babesia conradae is considered to be more pathogenic than *B. gibsoni*, resulting in higher parasitaemias and more severe anaemia [11].

6.1 Cardiac dysfunction

It's a rare complication of canine babesiosis; reported macroscopic cardiac lesions are effusions in pericardium, epicardial and endocardial haemorrhage involving one or more chambers with left ventricle being most commonly affected. Histopathological changes include necrosis, haemorrhage, fibrin micro-thrombi in the myocardium and inflammation. Lesions may be multifocal, but more generally they are limited to one area within the myocardium [41].

6.2 Consequence of canine babesiosis

Complicated babesiosis involves clinical manifestations that are not related to haemolytic disease. The most commonly documented complications include coagulopathy, ARF, ARDS, icterus and hepatopathy, haemoconcentration, immune-mediated haemolytic anaemia (IMHA), pancreatitis, hypotension, myocardial pathology, cerebral babesiosis and shock. Rare complications include gastrointestinal disturbance, myalgia, ocular involvement, upper respiratory signs, necrosis of the extremities and fluid accumulation. These complications can overlap.

7. Diagnosis

A precise and fast diagnosis and prompt treatment is required in critical situations such as hyperacute to acute phase of *B. canis* infection, where high mortality is generally reported.

7.1 Direct (microscopic) examination

Historically, *Babesia* infection in dogs was identified based on the morphologic appearance of the parasite in the erythrocyte; thus, microscopic evaluation for detecting intraerythrocytic parasites in Giemsa or Wright's stained blood smears remains the simplest, most accessible and reasonably sensitive especially during

acute infections. Differentiation between large and small piroplasms is also relatively simple. Moreover, in many parts of the developing world where babesiosis is endemic, microscopy is still the only viable available option. The likelihood of spotting a piroplasm increases with proper sampling technique, viz. sampling from capillary beds (ear tip, toe nail) or examination of cells from beneath the buffy coat of a haematocrit tube [37, 42] or search along the periphery of the blood smear, as parasitized red blood cells tend to marginate while making the smear. For diagnosis of large forms of *Babesia* (e.g. *B. canis*) from the majority of sick dogs, light microscopy is highly specific [2, 43], but small piroplasms (*B. gibsoni*, *B. microti*-like sp.) are hard to observe by light microscopy, which has a relatively poor to moderate sensitivity [44], and expertise is needed. Moreover due to very low, often intermittent parasitaemias, identification of piroplasms in chronically infected and carrier dogs remains a significant challenge.

Diagnosis is more problematic in chronic cases of infection due to less virulent species such as *B. canis* and *B. vogeli*, where parasitaemia may be below the microscopic detection limit, and in such cases thick smears (not alcohol fixed) may be helpful in detecting the parasite.

7.2 Haematological changes

The major haematological changes include mild to moderately regenerative normocytic and normochromic anaemia, leucocytosis with normal to decreased neutrophil counts and most consistent finding thrombocytopenia which is severe in the acute phase of infection [45].

7.3 Coagulation profiles

In a recent study, it was reported that there is significantly lower mean platelet count, prolonged activated partial thromboplastin time, higher fibrinogen concentrations and D-dimer value in infected dogs as compared to healthy controls [46].

7.4 Biochemical abnormalities

Elevation of liver enzymes such as ALP, ALT and AST. Elevated serum bilirubin concentration is associated with degree and rapidity of the anaemia and accompanying hepatopathy. There will be low total serum protein and albumin level in dogs with babesiosis. Urea is disproportionately raised to creatinine, and this is probably due to increased urea production resulting from gastrointestinal haemorrhage or protein catabolism as a result of febrile inflammatory illness [47, 48]. In complicated cases with renal dysfunction, there will be proportionate increase in serum urea and creatinine levels indicating decreased renal perfusion, as a result of hypovolaemia, decreased blood pressure and/or decreased myocardial function. Hypokalaemia has been reported in severely affected dog, it has not connected directly with babesiosis, and this could be attributed to decreased potassium intake. Considerable elevation of positive acute phase protein (α_1-acid glycoprotein) has been reported in dogs with *B. rossi* infection, but levels do not correlate with severity of disease or outcome [49].

7.5 Metabolic abnormalities

The most common complication is hypoglycaemia and is often associated with severe anaemia, icterus, young age (<6 months) and collapse [50]. Reduced survival has been associated with hypoglycaemia (<59.4 mg/dL) and hyperlactataemia.

Hypoglycaemia-induced central nervous system signs should not be misdiagnosed as cerebral babesiosis.

7.6 Electrocardiogram (ECG findings)

In canine babesiosis, variety of arrhythmias are reported including sinus arrest, sinoatrial block, first- and second-degree atrioventricular block, ventricular tachycardia and ventricular premature depolarizations. ECG abnormalities include prolonged QRS interval, low amplitude and notching of R waves, ST segment deviation and large T waves [41].

7.7 Urine analysis

Routine test may reveal presence of bilirubin, haemoglobin and protein in the urine. In a recent study conducted to assess renal dysfunction in *Babesia rossi*, infection revealed higher concentrations of urinary IgG, urinary CRP and urinary RBP suggestive of both glomerular and tubular dysfunction [51]. These can be used for early detection of *Babesia*-induced renal dysfunction than serum urea and creatinine and urine specific gravity. There will be minimum and variable changes in urine enzyme activity (GGT and ALP) in babesiosis, thus limiting their use as diagnostic tests [47].

7.8 Serological diagnosis

A recent study demonstrated the opportunity of an early and specific detection of acute infections by an AgELISA that is potentially translatable to a rapid diagnostic test design and can be used in an ELISA to detect circulating *Babesia* antigen during acute infections and can be used to detect parasites 24–48 h before it could be detected by light microscopy [52].

7.9 Molecular diagnosis

Molecular techniques help in refining the diagnosis to the species level and thus provide a more accurate prognosis. Different molecular techniques are used for identification and differentiation of the various species of *Babesia*, semi-nested PCR [53] reverse line blotting [9, 54] and PCR-restriction fragment length polymorphism analysis [55].

Improved PCR techniques have lately allowed for better definition of these parasites [56] and allows for a more reliable identification of the etiological agents compared to direct detection by light microscopy or serology [2]. It is more sensitive and provides an evidence of an active and ongoing infection in a clinical setting.

In addition, several genes are commonly used to discriminate among *Babesia* species. Typically, these include the nuclear ribosomal RNA genes [7, 8] and the two internal transcribed spacers (ITS1 and ITS2) [7]. PCR DNA amplification can be a useful technique for monitoring treatment [57].

7.10 Diagnostic imaging

The most consistent findings on abdominal ultrasonography in dogs with *B. canis* are hepatomegaly and splenomegaly with diffuse, hypoechoic, heterogeneity and renal changes like diffuse homogenous increased cortical echogenicity and increased corticomedullary definition [58]. Dogs infected with *B. rossi* and *B. canis* having gastrointestinal signs and abdominal pain are reported to have

ultrasonographic changes in the pancreases [32, 59] which are found to be consistent with acute pancreatitis and included duodenal atony and peripancreatic fat hyperechogenicity.

7.11 Differential diagnosis

It includes other causes of haemolytic anaemia such as haemobartonellosis, autoimmune haemolytic anaemia, pyruvate kinase deficiency and Heinz body haemolytic anaemia. Other differentials include immune-mediated thrombocytopenia, systemic lupus erythematosus, leptospirosis, rickettsial diseases, dirofilariasis with caval syndrome, leptospirosis, zinc toxicity and neoplasia.

8. Therapy

Treatment for canine babesiosis consists of three components:

- Treatment to eliminate the parasite
- Blood transfusions to treat severe anaemia
- Supportive care for the complications and metabolic derangements

8.1 Main drugs and drug combinations used in the antiprotozoal treatment of babesiosis

a. **Imidocarb dipropionate:** It is an aromatic diamidine and is recommended to be used as 6.6 mg/kg intramuscularly (IM) or subcutaneously (SC) with a repeated dose in 2 weeks in dogs. Among many of the proposed mechanisms of action includes blockage of the entry of inositol into erythrocytes containing *Babesia,* resulting in starvation of the parasite [60], interference with production [61] or combination with DNA in susceptible *Babesia* species, causing nucleic acid damage and inhibition of cellular repair and replication [62] (**Table 1**). It is approved for treatment of different forms of *Babesia* spp. [39, 57, 63]. The adverse effects of this medication include pain during injection and cholinergic effects such as salivation, drooling, nasal drip or vomiting which can be mitigated by premedicating with atropine at 0.05 mg/kg. Additionally some less frequent adverse effects are panting, restlessness, diarrhoea, renal tubular or hepatic necrosis and injection site inflammation and more rarely ulceration, which usually heals within days to weeks.

b. **Diminazene aceturate:** It is 4,4′-(diazoamino) dibenzamidine diaceturate which is widely used in tropical countries as a first-line agent for the treatment of *Babesia gibsoni* infection of dogs, usually as an intramuscular injection of 3.5 mg/kg. Although diminazene aceturate has anti-*Babesia* activity, it often fails to eliminate *B. gibsoni* from affected dogs and a relapse may occur. Furthermore, diminazene has a narrow clinical safety margin and can induce fatal nervous complications after 24–48 h of overdose. Clinical signs associated with diminazene toxicity are depression or stupor, continuous vocalisation, ataxia, opisthotonos, extensor rigidity, nystagmus and seizures [3]. There are reported toxicity such as acute CNS signs including ataxia, nystagmus and occasional seizures in dogs administered with one recommended intramuscular dose (3.5 mg/kg) of diminazene for treatment of babesiosis [64].

Babesia species	Drug	Dose and duration	Response to treatment
B. canis, *B. vogeli* and *B. rossi*	Imidocarb dipropionate	5–6.6 mg/kg IM once; may repeat in 14 days	Good
	Diminazene aceturate	A single dose of 3.5 mg/kg	
B. gibsoni	Azithromycin + atovaquone	10 mg/kg PO SID + 13.3 mg/kg PO TID for10 days	Improvement of anaemia and clinical signs without elimination of parasite and with occasional to frequent clinical relapses
	Clindamycin	12–25 mg/kg PO BID for 7–10 days	
B. conradae	Imidocarb dipropionate	5–6.6 mg/kg IM once; may repeat in 14 days	Moderate to poor with frequent relapses
B. microti-like	Imidocarb dipropionate	5–6.6 mg/kg IM once; may repeat in 14 days	Poor

Table 1.
Summary of the treatment protocols with antiprotozoal agents.

8.2 Combination therapies

a. **Atovaquone and azithromycin:** The first treatment that has been shown to be effective against *B. gibsoni* is a combination of an analog of ubiquinone, atovaquone (ATV) and a macrolide antibiotic, azithromycin (AZM) [57]. The use of ATV alone inhibits the growth of *Babesia* spp. and is presumed to act through blocking protozoan mitochondrial electron transport causing inhibition of pyrimidine and ATP synthesis [62]. Azithromycin acts by inhibiting the translation of mRNA and bacterial protein synthesis by binding to the 50S subunit of the prokaryote ribosome. It exerts its antiprotozoal effects by specifically acting on apicoplasts, a non-photosynthetic plastid organelles with a limited genome and found in apicomplexan parasites [65] including *Babesia* spp. [66]. In addition, the simultaneous use of ATV and AZM produces an additive or synergistic therapeutic effect, while the single use of each drug tends to result in a relapse of signs. Moreover possible emergence of drug-resistant variants of *B. gibsoni* can occur after the use of ATV alone, and these variants might be caused by mutations in the cytochrome b (CYTb) gene, resulting in amino acid substitutions at the putative ATV binding site [67]. Further, the results are not consistent based on molecular analysis [68].

b. **Buparvaquone and azithromycin:** Buparvaquone is a hydroxynaphthoquinone antiprotozoal drug-related to atovaquone and parvaquone. Buparvaquone (Butalex®) is used in the treatment of bovine theileriosis [69]. It is also used to treat *B. vulpes* infection in dogs at an off-label dose of 5 mg/kg IM twice 48 h apart, in combination with azithromycin at 10 mg/kgPO once daily for 10 days [63]. Buparvaquone's mode of action on piroplasms is probably comparable to atovaquone's.

c. **Combination therapy of clindamycin (CLDM), metronidazole (MNZ) and doxycycline (DOXY)** is an efficacious alternative treatment strategy for *B. gibsoni* infection [70]. However, this treatment takes a relatively long time to show its therapeutic effect [71].

8.3 Supportive treatment

Supportive therapy should be based on thorough patient assessment and should be provided for moderate-to-severe infection depending on the type of *Babesia* spp. infecting the dog which may include:

a. **Fluid therapy**: In *Babesia*-infected dogs, intravenous fluid therapy is required for patients in shock, old dogs with history of renal disease, clinically dehydrated patients and dogs with intravascular haemolysis and haemoglobinuria. Mildly dehydrated patients (approximately 5%) require 50 ml/kg body weight, and moderately dehydrated (approximately 10%) requires 100 ml/kg body weight, whereas severely dehydrated (15%) dogs require about 150 ml/kg body weight of replacement fluid. Usually intravenous crystalloid fluid is indicated with correction of electrolyte and acid–base abnormalities. It is important to maintain blood volume and adequate end-organ perfusion diuresis and prevention of red blood cell sludging in capillaries [72]. Hetastarch (10 to 20 ml/kg) causes greater plasma volumes expansion, its beneficial in resuscitative fluid therapy. As fluid therapy can exacerbate ARDS, close monitoring of respiratory rate and pulmonary sounds is crucial.

b. **Whole blood/ RBC/plasma transfusion:** Need for blood transfusion depends on magnitude of anaemia (haematocrit ≤15%) and clinical signs such as dyspnoea or tachypnoea. The degree of parasitaemia is not an important factor as it often bears little relation to the degree of anaemia. Packed erythrocytes (20 mL/kg) are the component of choice for treating haemolytic anaemia. Crossmatching is not mandatory for the first transfusion, as dogs do not have naturally occurring alloantibodies. Initially blood is transfused slowly at 2 ml/kg/h for the first 30–60 min while observing for transfusion reactions, such as a sudden rise in body temperature and/or respiratory rate and lip and ear pinna swelling. Infected dogs with disseminated intravascular coagulation or coagulation disorders may require plasma transfusions.

c. **Immunosuppressants:** The use of immunosuppressant drugs in dogs with immune-mediated haemolytic anaemia (IMHA) or thrombocytopenia is controversial because these conditions are always associated with infectious disease. But in cases of unresponsiveness to antiprotozoal treatment, the use of 2 mg/kg/day of prednisone is recommended in infected dogs with moderate-to-severe clinical signs [73].

d. **Other supportive therapies**: Other supportive therapies depend on the clinical signs and/or laboratory abnormalities, for example, oxygen therapy should be used when there is respiratory distress and antiemetics to counter vomiting. If the dog is stable and does not require hospitalization, then treatment should be restricted to antiprotozoal agents [74].

9. Prognostic indicators

In a recent study, it was suggested that lactate as a prognostic indicator with mean lactate in complicated cases of canine babesiosis wherein the blood lactate concentration in non-survivors (145 mg/dL) was higher than in survivors (13.8 mg/dL). Pretreatment hyperlactataemia (>45 mg/dL) and subsequent serial lactate concentrations that failed to return to normal reference range (persistently >40 mg/dL) indicate poor prognosis [75].

10. Prevention

The most effective preventive measures practised worldwide are regular control of the tick vectors by routinely dipping or spraying pets or using tick collars or spot-on preparations. As it takes a minimum of 48 hours for *Babesia* transmission, so regular examination of dogs for the presence of any ticks and to remove it soon after they attach is important. The merozoites circulating in the blood may be transmitted to a healthy host directly by blood transfusion, so blood donors should be screened negative for babesiosis, preferably by polymerase chain reaction. Moreover, it is also reported that *B. gibsoni* can be transmitted by transfer of blood during dog fighting, which should be prevented. In Europe a vaccine is available against *B. canis* with a reported efficacy of 70–100% [76]. More recently a bivalent vaccine called Pirodog® (Merial) derived from soluble parasite antigens from *B. canis* and *B. rossi* obtained from culture media supernatant has been shown to reduce duration and severity of clinical signs [77]. Although vaccination against canine babesiosis does not prevent infection, it does seem to block the initiation of pathologic processes involved in the pathogenesis of the disease [78]. This vaccine can be administered from 5 months of age and requires annual revaccination but does not cross-protect against other *Babesia* species. Vaccines against other *Babesia species* such as *B. gibsoni* are currently being developed including recombinant antigen and DNA vaccines [79–81]. Although dogs can be vaccinated, the level of protection is highly variable, which might be due to genetic diversity of *B. canis* strains.

11. Conclusion

The spectrum of *Babesia* pathogens that infect dogs is gradually being elucidated with the aid of new molecular techniques and meticulous clinical investigation. Species of *Babesia* that cannot be distinguished morphologically cause diverse diseases and are transmitted by different vector ticks. Nonvector transmission by blood transfusion and directly from dog to dog is of special concern and could be responsible for the spread of infection to areas that were previously non-endemic. Correctly identifying the infectious agent is important for treatment planning and prognosis.

Acknowledgements

We would like to acknowledge the Department of Veterinary Medicine, Veterinary College, Bangalore, India.

Conflict of interest

The authors declare that there is no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.82243

Author details

Poonam Vishwakarma[1*] and M.K. Nandini[2]

1 Biosafety Support Unit, Government of India, New Delhi, India

2 My Pet's Çhoice, The Companion Animal Clinic, Bangalore, India

*Address all correspondence to: drpoonamvet@gmail.com

References

[1] Irwin PJ. Canine babesiosis: From molecular taxonomy to control. Parasites & Vectors. 2009;**2**(Suppl 1):S4

[2] Solano-Gallego L, Baneth G. Babesiosis in dogs and cats-expanding parasitological and clinical spectra. Veterinary Parasitology. 2011;**18**:48-60

[3] Boozer AL, Macintire DK. Canine babesiosis. The Veterinary Clinics of North America. Small Animal Practice. 2003 Jul;**33**(4):885-904

[4] Baneth G, Florin-Christensen M, Cardoso L, Schnittger L. Reclassification of Theileria annae as *Babesia vulpes* sp. nov. Parasites & Vectors. 2015;**8**:207

[5] Reichenow E. Übertagungsweise und Entwicklung der Piroplasmen. ZENTRALBLATT FUR BAKTERIOLOGIE MIKROBIOLOGIE UND HYGIENE SERIE B. 1935;**135**:108-199

[6] Reichenow E. Über die Entwicklung von Theileriaparva, demErreger des Küstenfiebers der Rinder, in Rhipicephalus appendiculatus. ZENTRALBLATT FUR BAKTERIOLOGIE MIKROBIOLOGIE UND HYGIENE SERIE B. 1937;**140**:223-226

[7] Zahler M, Schein E, Rinder H, Gothe R. Characteristic genotypes discriminate between *Babesia canis* isolates of differing vector specificity and pathogenicity in dogs. Parasitology Research. 1998;**84**:544-548

[8] Carret C, Walas F, Carcy B, Grande N, Precigout E, Moubri K, et al. *Babesia canis canis, Babesia canis vogeli, Babesia canis rossi*: Differentiation of the three subspecies by a restriction fragment length polymorphism analysis on amplified small subunit ribosomal RNA genes. The Journal of Eukaryotic Microbiology. 1999;**46**:298-303

[9] Matjila PT, Penzhorn BL, Bekker CP, Nijhof AM, Jongejan F. Confirmation of occurrence of *Babesia canis vogeli* in domestic dogs in South Africa. Veterinary Parasitology. 2004;**122**:119-125

[10] Muhlnickel CJ, Jefferies R, Morgan-Ryan UM, Irwin PJ. *Babesia gibsoni* infection in three dogs in Victoria. Australian Veterinary Journal. 2002;**80**:606-610

[11] Kjemtrup AM, Wainwright K, Miller M, Penzhorn BL, Carreno RA. *Babesia conradae*, sp. nov., a small canine Babesia identified in California. Veterinary Parasitology. 2006;**138**:103-111

[12] Camacho AT, Pallas E, Gestal JJ, Guitian FJ, OlMeda AS, Telford SR, et al. Ixodes hexagonus is the main candidate as vector of Theileria annae in Northwest Spain. Veterinary Parasitology. 2003;**112**:157-163

[13] Kalra IS, Sing KB. Observations of naturally occurring Babesia canis infection in dog. The Indian Veterinary Journal. 1984;**61**:98-100

[14] Varshney JP, Kumar A, Hoque M. *Ehrlichia platys* and *Babesia canis* infection in a dog: A clinical report. Journal of Veterinary Parasitology. 2004;**18**:35-37

[15] Sinha BP, Ghosh P. Treatment of clinical cases of canine babesiosis. Indian Journal of Veterinary Medicine. 1986;**6**:94

[16] Varshney JP, Varshney VP, Hoque M. Clinico-haematological, biochemical, endocrinological and ultrasonographic findings in canine babesiosis. The Indian Journal of Animal Sciences. 2003;**73**:1099-1101

[17] Homer MJ, Aguilar-Delfin I, Telford SR, Krause PJ, Persing DH.

Babesiosis. Clinical Microbiology Reviews. 2000;**13**:451-469

[18] Lempereur L, De Cat A, Caron Y, Madder M, Claerebout E, Saegerman C, et al. First molecular evidence of potentially zoonotic *Babesia microti* and Babesia sp. EU1 in *Ixodes ricinus* ticks in Belgium. Vector Borne and Zoonotic Diseases. 2011;**11**:125-130

[19] Lobetti RG. Babesiosis. In: Greene CE, editor. Infectious Diseases of the Dog and Cat. 3rd ed. Philadelphia: W.B. Saunders; 2006

[20] LaiaSolano-Gallego ÁS, Roura X, Estrada-Peña A, Miró G. A review of canine babesiosis: The European perspective. Parasites & Vectors. 2016;**9**:336. DOI: 10.1186/s13071-016-1596-0

[21] Birkenheuer AJ, Correa MT, Lev MG, Breitschwerdt EB. Geographic distribution of babesiosis among dogs in the United States and association with dog bites: 150 cases (2000-2003). Journal of the American Veterinary Medical Association. 2005;**227**:942-947

[22] Yeagley TJ, Reichard MV, Hempstead JE, Allen KE, Parsons LM. Detection of *Babesia gibsoni* and the canine small Babesia 'Spanish isolate' in blood samples obtained from dogs confiscated from dogfighting operations. Journal of the American Veterinary Medical Association. 2009;**235**:535-539

[23] Mierzejewska EJ, Welc-Faleciak R, Bednarska M, Rodo A, Bajer A. The first evidence for vertical transmission of *Babesia canis* in a litter of central Asian shepherd dogs. Annals of Agricultural and Environmental Medicine. 2014;**21**:500-503

[24] Simoes PB, Cardoso L, Araujo M, Yisaschar-MekuzasY, BanethG. Babesiosis due to the canine Babesia microti-like small piroplasm in dogs-first report from Portugal and possible vertical transmission. Parasites & Vectors. 2011;**4**:50

[25] Stegeman JR, Birkenheuer AJ, KrugerJM, BreitschwerdtEB. Transfusion associated *Babesia gibsoni* infection in a dog. Journal of the American Veterinary Medical Association. 2003;**222**:959-963

[26] Jefferies R, Ryan UM, Jardine J, Broughton DK, Robertson ID, Irwin PJ. Blood, bull terriers and babesiosis: Further evidence for direct transmission of *Babesia gibsoni* in dogs. Australian Veterinary Journal. 2007;**85**:459-463

[27] Taboada J, Merchant SR. Babesiosis of companion animals and man. Veterinary Clinics of North America: Small Animal Practice. 1991;**21**:103-123

[28] Taboada J. Babesiosis. In: Greene CE, editor. *Infectious Diseases of the Dog and Cat*. Philadelphia: WB Saunders; 1998. pp. 473-481

[29] Wozniak EJ, Barr BC, Thomford JW, et al: Clinical, anatomic, and Immunopathologic characterization of *Babesia gibsoni* infection in the domestic dog (*Canis Familiaris*). The Journal of Parasitology 1997;**83**(4):692-699

[30] Jacobson LS, Clark IA. The pathophysiology of canine Babesiosis: New approaches to an old puzzle. Journal of the South African Veterinary Association. 1994;**65**:134-145

[31] Máthé A, Dobos-Kovacs M, Voros K. Histological and ultra-structural studies of renal lesions in *Babesia canis* infected dogs treated with imidocarb. Acta Veterinaria Hungarica. 2007;**55**:511-523. DOI: 10.1556/AVet.55.2007.4.10

[32] Mohr AJ, Lobetti RG, VanDerlugt JJ. Acute pancreatitis: A newly recognized potential

complication of canine babesiosis. Journal of the South African Veterinary Association. 2000;**71**:232-239

[33] Leisewitz AL, Jacobson LS, De Morais HS, Reyers F. The mixed acid-base disturbances of severe canine babesiosis. Journal of Veterinary Internal Medicine. 2001;**15**:445-452

[34] Keller N, Jacobson LS, Nel M, De Clerq M, Thompson PN, Schoeman JP. Prevalence and risk factors of hypoglycemia in virulent canine babesiosis. Journal of Veterinary Internal Medicine. 2004;**18**:265-270

[35] Jacobson LS. The south African form of severe and complicated canine babesiosis: Clinical advances 1994-2004. Veterinary Parasitology. 2006;**138**:126-139

[36] Welzl C, Leisewitz AL, Jacobson LS, Vaughanscott T, Myburgh E. Systemic inflammatory response syndrome and multiple-organ damage/dysfunction in complicated canine babesiosis. Journal of the South African Veterinary Association. 2001;**72**:158-162

[37] Irwin PJ, Hutchinson GW. Clinical and pathological findings of *Babesia* infection in dogs. Australian Veterinary Journal. 1991;**68**:204-209

[38] Furlanello T, Fiorio F, Caldin M, Lubas G, Solano-Gallego L. Clinicopathological findings in naturally occurring cases of babesiosis caused by large form *Babesia* from dogs of northeastern Italy. Veterinary Parasitology. 2005;**134**:77-85

[39] Conrad P, Thomford J, Yamane I, Whiting J, Bosma L, Uno T, et al. Hemolytic anemia caused by *Babesia gibsoni* infection in dogs. Journal of the American Veterinary Medical Association. 1991;**199**:601-605

[40] MacIntire DK, Boudreaux MK, West GD, Bourne C, Wright JC, Conrad PA. *Babesia gibsoni* infection among dogs in the southeastern United States. Journal of the American Veterinary Medical Association. 2002;**220**:325-329

[41] Dvir E, Lobetti RG, Jacobson LS, Pearson J, Becker PJ. Electrocardiographic changes and cardiac pathology in canine babesiosis. Journal of Veternary Cardiology. 2004;**6**(1):15-23

[42] Böhm M, Leisewitz AL, Thompson PN, Schoeman JP. Capillary and venous *Babesia canis rossi* parasitaemias and their association with outcome of infection and circulatory compromise. Veterinary Parasitology. 2006;**141**:18-29

[43] Solano-Gallego L, Trotta M, Carli E, Carcy B, Caldin M, Furlanello T. *Babesia canis canis* and *Babesia canis vogeli* clinicopathological findings and DNA detection by means of PCR-RFLP in blood from Italian dogs suspected of tick-borne disease. Veterinary Parasitology. 2008;**157**:211-221

[44] Miro G, Checa R, Paparini A, Ortega N, Gonzalez-Fraga JL. Theileria annae (syn. Babesia microti-like) infection in dogs in NW Spain detected using direct and indirect diagnostic techniques: Clinical report of 75 cases. Parasites & Vectors. 2015;**8**:217

[45] Scheepers E, Leisewitz AL, Thompson PN, Christopher MM. Serial haematology results in transfused and non-transfused dogs naturally infected with *Babesia rossi*. Journal of the South African Veterinary Association. 2011;**82**(3):136-143

[46] Liebenberg C, Goddard A, Wiinberg B, et al. Hemostatic abnormalities in uncomplicated babesiosis (*Babesia rossi*) in dogs. Journal of Veterinary Internal Medicine. 2013;**27**(1):150-156

[47] Lobetti RG, Jacobson LS. Renal involvement in dogs with babesiosis.

Journal of the South African Veterinary Association. 2001;**72**(1):23-28

[48] Reyers F. Is the Azotaemia in Canine Babesiosis an Indication of Renal Disease. 9th Faculty Day, University of Pretoria, Faculty of Veterinary Science. 1992. p. 17

[49] Lobetti RG, Mohr AJ, Dippenaar T, Myburgh E. A preliminary study on the serum protein response in canine babesiosis. Journal of the South African Veterinary Association. 2000;**71**(1):38-42

[50] Keller N, Jacobson LS, Nel M, et al. Prevalence and risk factors of hypoglycemia in virulent canine babesiosis. Journal of Veterinary Internal Medicine. 2004;**18**(3):265-270

[51] Defauw P, Schoeman JP, Smets P, et al. Assessment of renal dysfunction using urinary markers in canine babesiosis caused by *Babesia rossi*. Veterinary Parasitology. 2012;**190**(3-4):326-332

[52] Eichenberger RM, Štefanić S, Naucke TJ, Šarkūnas M, Zamokase G, Grimma F, et al. An ELISA for the early diagnosis of acute canine babesiosis detecting circulating antigen of large Babesia spp. Veterinary Parasitology. 2017;**243**:162-168. http://dx.doi.org/10.1016/j.vetpar.2017.06.030

[53] Birkenheuer AJ, Levy MG, Breitschwerdt EB. Development and evaluation of a semi nested PCR for detection and differentiation of *Babesia gibsoni* (Asian genotype) and *B. canis* DNA in canine blood samples. Journal of Clinical Microbiology. 2003;**41**:4172-4177

[54] Yisaschar-Mekuzas Y, Jaffe CL, Pastor J, Cardoso L, Baneth G. Identification of Babesia species infecting dogs using reverse line blot hybridization for six canine piroplasms, and evaluation of co-infection by other vector-borne pathogens. Veterinary Parasitology. 2013;**191**:367-373

[55] Jefferies R, Ryan UM, Irwin PJ. PCR-RFLP for the detection and differentiation of the canine piroplasm species and its use with filter paper-based technologies. Veterinary Parasitology. 2007;**144**:20-27

[56] Matjila PT, Leisewitz AL, Jongejan F, Penzhorn BL. Molecular detection of tick-borne protozoal and ehrlichial infections in domestic dogs in South Africa. Veterinary Parasitology. 2008;**155**:152-157

[57] Birkenheuer AJ, Levy MG, Breitschwerdt EB. Efficacy of combined atovaquone and azithromycin for therapy of chronic *Babesia gibsoni* (Asian genotype) infections in dogs. Journal of Veterinary Internal Medicine. 2004;**18**(4):494-498

[58] Fraga E, Barreiro JD, Goicoa A. Abdominal ultrasonographic findings in dogs naturally infected with babesiosis. Veterinary Radiology & Ultrasound. 2011;**52**(3):323-329

[59] Mathe A, Voros K, Papp L, Reiczigel J. Clinical manifestations of canine babesiosis in Hungary (63 cases). Acta Veterinaria Hungarica. 2006;**54**(3):367-385

[60] McHardy N, Woollon RM, Clampitt RB, James JA, Crawley RJ. Efficacy, toxicity and metabolism of imidocarb dipropionate in the treatment of *Babesia ovis* infection in sheep. Research in Veterinary Science. 1986;**41**:14-20

[61] Bacchi CJ, Nathan HC, Hutner SH, Duch DS, Nichol CA. Prevention by polyamines of the curative effect of amicarbalide and imidocarb for *Trypanosoma brucei* infections in mice. Biochemical Pharmacology. 1981;**30**:883-886

[62] Plumb DC: Plumb's Veterinary Drug Handbook, 8th edition. Wiley-Blackwell, Ames; 2015. pp. 1296

[63] Checa R, Montoya A, Ortega N, González-Fraga JL, Bartolomé A, Gálvez R. Marino V and Miró, G: Efficacy, safety and tolerance of imidocarb dipropionate versus atovaquone or buparvaquone plus azithromycin used to treat sick dogs naturally infected with the *Babesia microti*-like piroplasm. Parasites & Vectors. 2017;**10**:145

[64] Han D, Yoon W-K, Hyun C. Cerebellar encephalopathy from diminazene aceturate (beneril)toxicity in a dog. Korean Journal of Veterinary Research. 2014;**54**(3):193-196. http://dx.doi.org/10.14405/kjvr.2014.54.3.193

[65] Chakraborty A. Understanding the biology of the *Plasmodium falciparum* apicoplast;an excellent target for antimalarial drug development. Life Sciences. 2016;**158**:104-110

[66] Wang T, Guan G, Korhonen PK, Koehler AV, Hall RS, Young ND, et al. The apicoplast genomes of two taxonomic units of *Babesia* from sheep. Veterinary Parasitology. 2017;**233**:123-128

[67] Sakuma M, Setoguchi A, Endo Y. Possible emergence of drug-resistant variants of *Babesia gibsoni* in clinical cases treated with atovaquone and azithromycin. Journal of Veterinary Internal Medicine 2009;**23**:493-498

[68] Jefferies R, Ryan UM, Jardine J, et al. *Babesia gibsoni*: Detection during experimental infections and after combined atovaquone and azithromycin therapy. Experimental Parasitology. 2007;**117**:115-123

[69] Wilkie GM, Brown CG, Kirvar BE, Thomas M, Williamson SM, Bell-Sakyi LJ, et al. Chemoprophylaxis of *Theileria annulata* and *Theileria parva* infections of calves with buparvaquone. Veterinary Parasitology. 1998;**78**:1-12

[70] Nandini MK, Vishwakarma P, Kamran CA. New therapeutic protocol for canine babesiosis: A case report. Journal of Dairy, Veterinary & Animal Research. 2016;**3**(3):112-113. DOI: 10.15406/jdvar.2016.03.00082

[71] Suzuki K, Wakabayashi H, Takahashi M, et al. A possible treatment strategy and clinical factors to estimate the treatment response in *Babesia gibsoni* infection. The Journal of Veterinary Medical Science. 2007;**69**(5):563-568

[72] Ayoob AL, Hackner SG, Prittie J. Clinical management of canine babesiosis. Journal of veterinary emergency and critical care (San Antonio). 2010;**20**:77-89

[73] Grundy SA, Barton C. Influence of drug treatment on survival of dogs with immune-mediated hemolytic anemia: 88 cases (1989-1999). Journal of the American Veterinary Medical Association. 2001;**218**:543-546

[74] Kidd L, Mackman N. Prothrombotic mechanisms and anticoagulant therapy in dogs with immune-mediated hemolytic anemia. Journal of Veterinary Emergency and Critical Care (San Antonio, Tex.). 2013;**23**:3-13

[75] Nel M, Lobetti RG, Keller N, Thompson PN. Prognostic value of blood lactate, blood glucose, and Hematocrit in canine Babesiosis. Journal of Veterinary Internal Medicine. 2004;**18**:471-476

[76] Moreau Y, Vidor E, Bissuel G. DubreuilN: Vaccination against canine babesiosis: An overview of field observations. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1989;**83**(Suppl):95-96

[77] Schetters TP, Kleuskens J, Carcy B, Gorenflot A, Vermeulen A. Vaccination against large *Babesia* species from dogs. Parasitologia. 2007;**49**(Suppl 1):13-17

[78] Schetters TP, Kleuskens JA, Scholtes NC, Pasman JW, Goovaerts D. Vaccination of dogs against *Babesia canis* infection. Veterinary Parasitology. 1997;**73**(1-2):35-41

[79] Fukumoto S, Tamaki Y, Igarashi I, Suzuki H, Xuan X. Immunogenicity and growth inhibitory efficacy of the prime-boost immunization regime with DNA followed by recombinant vaccinia virus carrying the P29 gene of *Babesia gibsoni* in dogs. Experimental Parasitology. 2009;**123**:296-301

[80] Fukumoto S, Tamaki Y, Okamura M, Bannai H, Yokoyama N, Suzuki T, et al. Prime boost immunization with DNA followed by a recombinant vaccinia virus expressing P50 induced protective immunity against *Babesia gibsoni* infection in dogs. Vaccine. 2007;**25**:1334-1341

[81] Fukumoto S, Tamaki Y, Shirafuji H, Harakawa S, Suzuki H, Xuan X. Immunization with recombinant surface antigen P50 of *Babesia gibsoni* expressed in insect cells induced parasite growth inhibition in dogs. Clinical and Diagnostic Laboratory Immunology. 2005;**12**:557-559