

# Atovaquone as an Alternative Therapeutic Management for Babesiosis in Canine

Vishnu Kumar Rai<sup>1</sup>, Arbind Singh<sup>2\*</sup>, Amit Kumar Verma<sup>3</sup>, Prem Sagar Maurya<sup>4</sup>, Vikas Jaiswal<sup>5</sup>, Tarun Kumar<sup>6</sup> and Aditya Kumar<sup>7</sup>

<sup>1</sup>MVSc Scholar, Veterinary Medicine, Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut, Uttar Pradesh -250110, INDIA

<sup>2</sup>Assistant Professor, Livestock Farm Complex (Veterinary Medicine), Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut, Uttar Pradesh -250110, INDIA

<sup>3</sup>Professor & Head, Veterinary Medicine, Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut, Uttar Pradesh -250110, INDIA

<sup>4</sup>Associate Professor, Veterinary Parasitology, Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut, Uttar Pradesh -250110, INDIA

<sup>5</sup>Assistant Professor, Veterinary Pathology, Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut, Uttar Pradesh -250110, INDIA

<sup>6</sup>MVSc Scholar, Veterinary Medicine, Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut, Uttar Pradesh -250110, INDIA

<sup>7</sup>PhD Scholar, Veterinary Medicine, G.B. Pant University of Agriculture and Technology, Pantnagar, U.S. Nagar(Uttarakhand)-263145, INDIA

\*Corresponding Author: [arvindsingh80279@gmail.com](mailto:arvindsingh80279@gmail.com)

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## Abstract

*Canine Babesiosis is a significant tick-borne haemoprotozoan infection caused by the intra-erythrocytic parasite Babesia species. It commonly presents with fever, haemolytic anaemia, thrombocytopenia, and splenomegaly. A six-month-old female German shepherd was brought to the Veterinary Clinical Complex, Meerut, with anorexia, tachypnoea, and tick infestation. Clinical examination revealed weakness, depression, and a fever of 105.2 °F. Blood tests showed anaemia, hemoglobinemia, and thrombocytopenia, while a thin blood smear confirmed Babesia infection. Initial treatment included Doxycycline (10 mg/kg orally every 24 hours) with supportive therapy for seven days. While the dog showed slight improvement, Babesia species persisted in the blood smear. Consequently, the treatment was revised to Azithromycin (10 mg/kg orally every 24 hours) and Atovaquone (13.3 mg/kg orally every 8 hours) for ten days. This led to full recovery, with the dog regaining appetite, resolving fever, and showing no parasitaemia on follow-up blood tests.*

**Keywords:** Atovaquone, Azithromycin, Babesiosis, Doxycycline, German Shepherd Dog.

## Introduction

Babesiosis is a globally significant haemoprotozoan parasitic disease affecting vertebrates, primarily transmitted by ticks. This disease poses a considerable risk to cattle, small ruminants, and dogs, particularly in tropical and subtropical regions (Kumar *et al.*, 2024). Ticks serve as the main vectors for the transmission of the parasite (Singh *et al.*, 2023, 2024; Kumar *et al.*, 2024), and it has been reported to be endemic in regions such as Asia, Africa, Europe, and North America. The disease is caused by an obligate intra-erythrocytic parasite belonging to the *Babesia* genus, which is typically characterized as a pear-shaped apicomplexan and often appears in pairs (Irwin, 2009; Aleem *et al.*, 2024). Clinical manifestations include lethargy, cachexia, fever, respiratory distress, jaundice, hepatomegaly, splenomegaly and severe haemolytic illness. Additionally, this disease is linked to auto-immune haemolytic anaemia (Conrad *et al.*, 1991; Kumar *et al.*, 2023). The incubation period for Babesiosis ranges from 10 to 28 days and it is recognized as a zoonotic disease (Azhar *et al.*, 2023).

The traditional approach, exemplified by Geimsa's staining, is typically effective in identifying acute infections; however, it proves to be less sensitive in detecting carrier animals, particularly when parasitaemia level is low (Arif *et al.*, 2024). Giemsa staining is a cost-efficient direct microscopic method commonly utilized in field studies to examine a substantial number of suspected cases, facilitating the identification of piroplasm in smears prepared from whole blood (Aktas *et al.*, 2007; Singh *et al.*, 2023). Subclinical infections can be identified through serological tests such as indirect fluorescent antibody testing (IFAT), capillary tube agglutination (CA), indirect haemagglutination assay (IHA), and ELISA, making them valuable for epidemiological research (Molad *et al.*, 2006; Gubbels *et al.*, 2000). The conventional treatment involves use of Clindamycin and Quinine, however, this approach often leads to adverse effects and may not always be effective (Ji *et al.*, 2024). Therefore, an efficient therapeutic drug is still required to treat canine babesiosis particularly to address the recurrent infection caused by *B. gibsoni*. Although an encourage in alternative treatment option is the combination of atovaquone and Azithromycin (Krause *et al.*, 2000). Currently, there is no documented evidence of side effects associated with the use of Atovaquone in dogs (Cohn *et al.*, 2011). Atovaquone is a synthetic hydroxy-1,4-naphthoquinone anti-protozoal drug that specially inhibits mitochondrial electron transport, thereby disrupting pyrimidine and ATP synthesis (Sykes *et al.*, 2021).

## Case History and Clinical Observations

A six-year-old female German shepherd dog was presented with a history of reduced appetite and lethargy accompanied by a single episode of vomiting over the last one week. The owner observed that the dog had been rubbing against the wall for several days, after which a few ticks were found in that area. The dog had received timely deworming and vaccinations with no previous history of illness. The local Veterinarian treated patient with Doxycycline at a dosage of 10 mg/kg body weight orally every 24 hours, in addition to symptomatic treatment. However, the owner reported no significant improvement in the dog's condition. Upon examination at the clinic on the first day, the dog appeared depressed and lethargic (Figure 1 a) and exhibited pale mucous membranes in the gums (Figure 2 b).



Figure 1(a) Depressed and lethargic



Figure 1 (b) Pale mucus membrane of gums

## Clinical Examination

Clinical assessment indicated the presence of pale mucus membrane, Significant dehydration exceeding 5%, elevated rectal temperature of 105°F, tachycardia at 120 beats per minute, and tachypnoea at 37 breaths per minute.

Additionally, there was an enlargement of the popliteal lymph node and a cutaneous resuscitation time exceeding 4 seconds. Ticks were observed on the dorsal surface of the dog. An ultrasonographic evaluation showed mild splenomegaly and hepatomegaly, as well as signs of constipation.

## Laboratory Examination

Peripheral thin blood smears were prepared following standard protocols, subsequently fixed and stained using Giemsa stain. The smears were examined under an oil immersion lens at magnification of 100 X to identify hemoprotozoan organisms (Potgieter *et al.*, 2004). The examination of the blood revealed the presence of *Babesia* spp. parasites within red blood corpuscles, accompanied by spherocytes, suggestive of auto-immune haemolytic anaemia. Whole blood collected in an EDTA vial at a concentration of 1 mg/ml was analyzed for various haematological parameters, including haemoglobin (Hb), total erythrocyte count (TEC), total leukocyte count (TLC), differential leukocyte count (DLC), packed cell volume (PCV), and platelet count (Schalm *et al.*, 1975). The result indicated anaemia, hemoglobinemia, thrombocytopenia (Table 1). A slide agglutination test conducted with normal saline resulted in agglutination.

**Table 1:** Haematological parameters of dog affected with *Babesia* Spp. infection.

S.N.	Parameters	Unit	Day-1 Values	Day-11 Values	Reference Range
1.	Haemoglobin	gm/dl	4.6	13.6	12.0-18.0
2.	Packed Cell Volume (PCV)	%	11.2	40.2	33.0-55.0
3.	Total Erythrocyte Count (TEC)	10 <sup>6</sup> /μl	1.94	6.9	5.5-8.5
4.	Total Leucocyte Count (TLC)	10 <sup>3</sup> / μl	23.81	15.57	6.0-17.0
5.	Neutrophil	%	80.2	67.4	60.0-72.0
6.	Lymphocyte	%	7	22.9	12.0-30.0
7.	Eosinophil	%	5	5.4	2.0-10.0
8.	Basophil	%	0	0	Rare
9.	Monocyte	%	7.8	4.3	3.0-10.0
10.	Total Platelet Count	10 <sup>5</sup> / μl	0.53	2.82	2.0-9.0

#Reference range adopted from Schalm *et. al.*, 1975

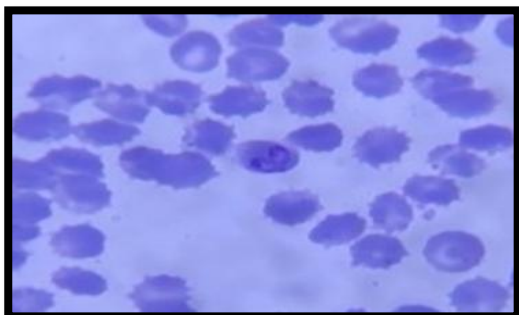
**Complete Blood Count Report:** Depicting Hemoglobinemia, low PCV indicating severe dehydration low total erythrocyte count indicating anaemia and low total platelet count indicating thrombocytopenia.

## Treatment

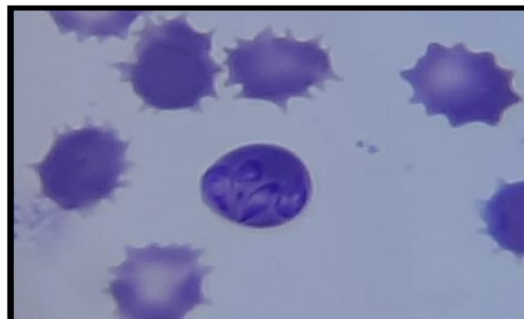
The treatment plan primarily aimed to manage parasitaemia, while addressing haemolytic anaemia and fever. The prescribed medications included Atovaquone at a dose rate of 13.3 mg/kg body weight orally every eight hours, with a fatty meal, along with Azithromycin at a dose rate of 10 mg/kg body weight every 24 hours for ten days. Inj. Prednisolone acetate was administered intramuscularly for three days at a dose rate of 1.1 mg/kg body weight on the first day, followed by a tapering regimen over the subsequent two days to manage immune-mediated auto haemolytic anaemia. Supportive treatment included fluid therapy with Inj. Normal saline at a rate of 10ml/kg body weight and Inj. Ringer Lactate at 15 ml/kg body weight, both administered intravenously for two days. Additionally, Inj. Meloxicam was given intramuscularly at a dosage of 0.3 mg/kg body weight, along with Inj. pantoprazole at 1 mg/kg body weight intravenously, and Inj. Ethamsylate at a total dose of 500 mg intravenously for three consecutive doses. Following the administration of meloxicam, the dog's body temperature decreased to 101°F within one hour. For liver support, Syp. Liv. 52 was provided at a dosage of 10 ml orally every 12 hours, in conjunction with Syp. Rubiriseat 5 ml orally every 12 hours. The owner was advised to apply anti-tick shampoo weekly for three weeks. The dog exhibited a return to normal feeding behaviour within one week of treatment. A complete blood count and thin blood smear examination conducted on the 11<sup>th</sup> day revealed all parameters to be within normal limits, with no evidence of *Babesia* spp. parasites in the erythrocytes. The owner was also advised to conduct regular general examinations of her pet.

## Results and Discussion

*Babesia* spp. are large piroplasm characterized by a pyriform shape, measuring 4-5  $\mu\text{m}$  in length, with one end pointed and the other rounded. Typically, one, two or four organisms can be found within individual erythrocytes, although instances of more than 16 organisms within a single red blood cell have been documented. The presence of *Babesia* spp. in erythrocytes can be confirmed through microscopic examination using a Giemsa-stained thin blood smear. *Babesia* spp. Exhibit both four pear-shaped forms (Figure 2 a) and two pear-shaped forms (Figure 2 b) within the erythrocytes.



**Figure 2 (a)** Four Pear-shaped

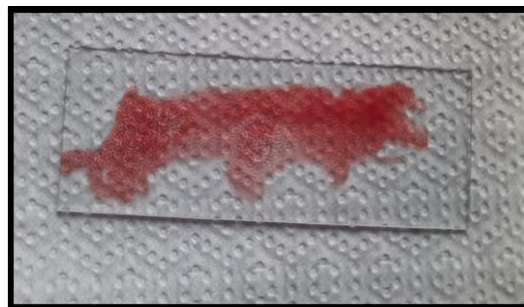


**Figure 2 (b)** Two pear-shaped, intra-erythrocytic piroplasm of *Babesia* spp. in Giemsa-stained thin blood smears

Agglutination of erythrocytes leads to the formation of irregular spherical clumps of cells, ranging from two to numerous, due to the bridging of erythrocytes by antibody. This phenomenon is highly indicative of immune mediated haemolytic anaemia, although it may also occur following a mismatched blood transfusion. To verify the occurrence of agglutination, one can mix a small sample of blood with a drop of isotonic saline, agglutination will remain evident, whereas rouleaux will separate. In some cases, agglutination may be pronounced enough to be visibly observed on a blood film and along the sides of the EDTA tube.



**Figure 3 (a)** Positive slide agglutination test confirming haemolysis



**Figure 3 (b)** Spherocytes in Giemsa-stained thin blood smears indicating immune-mediated haemolytic anaemia

Canine Babesiosis is clinically identified by the presence of haemolytic anaemia, thrombocytopenia, and fever. The increase in parasitaemia leads to heightened osmotic fragility of erythrocytes, resulting in haemolysis due to both serum haemolytic factors and the parasitic infection (Jacobson *et al.*, 1994; Singh *et al.*, 2024). Traditional treatments utilizing Imidocarb dipropionate and Diminazene aceturate have been associated with cerebral toxicity and have proven ineffective in eradicating the parasite from the host (Nayyar Ghauri *et al.*, 2019). The combination therapy of Atovaquone-Azithromycin has demonstrated significant efficacy in alleviating the nonspecific symptoms associated Babesiosis. Additionally, Prednisolone acetate has been administered to mitigate auto-immune haemolysis. Atovaquone act as a selective inhibitor of the mitochondrial electron transport system in the parasite, while Azithromycin effectively targets all developmental stages within the bloodstream and disrupts apicoplast function. Consequently, the Atovaquone-Azithromycin combination presents a viable and more effective alternative treatment of Babesiosis in canines.

## Conclusion

In the present investigation, canine babesiosis was managed using Atovaquone ~~tablets~~ administered at a dose rate of 13.3 mg/kg body weight orally every eight hours, accompanied by a fatty meal. This was combined with Azithromycin at a dose rate of 10 mg/kg of body weight orally every 24 hours over ten days. The pet owner was instructed to use anti-tick shampoo every week for three weeks. Within one week of initiating treatment, the dog returns to normal feeding habits. A complete blood count and thin blood smear analysis performed on the 11th day indicated that all parameters were within normal ranges, with no evidence of *Babesia* spp. parasites in the erythrocytes. The treatment regimen of Atovaquone and Azithromycin resulted in complete recovery over the ten-day therapy period. It can be concluded that canine babesiosis, which is prevalent in dogs, can be effectively treated with the outlined therapeutic approach without any adverse side effects.

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## Contribution by Authors

Each co-author contributes equally.

## Conflict of Interests

There is no conflict of interest.

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