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Review Article

# Literature Study: Babesiosis in Dogs in The Period of 2013-2023

## Studi Literatur: Babesiosis pada Anjing pada Periode 2013-2023

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## ABSTRACT

**Background:** Babesiosis is an infectious disease caused by *Babesia spp.* with tick vectors *Rhipicephalus sanguineus* and *Dermacentor margniatus* (a tick-borne disease). Babesiosis transmission occurs through tick bites or blood transfusions. Diagnostic techniques involve the microscopic examination of blood smears, hematology, blood chemistry, and PCR laboratory analysis. **Objective:** To determine the clinical symptoms, confirmation of diagnosis, and therapy used for babesiosis conditions in dogs. **Method:** Analysis was conducted on 22 literature cases of babesiosis in dogs with a publication period of 2013-2023. The analysis was carried out using the descriptive analysis method, a problem-solving procedure that describes the condition of the subject or object based on facts, characteristics, and any relationships between the phenomena being investigated. Qualitative research methods were used to examine natural object conditions, as a key instrument. Data source sampling was done purposively, the data collection techniques were combined, the data analysis was either inductive or qualitative, and qualitative research results emphasize meaning. **Result:** Dog patients with babesiosis have the highest prevalence of clinical symptoms, namely anorexia (62.5%), vomiting (33.3%), pyrexia (54.16%) lethargy (45.83%), brownish urination (29.16%), and ectoparasite infestation (29.16%). Confirmation of the diagnosis carried out included the microscopic examination of blood smears (100%), hematology (91.66%), blood chemistry (41.66%), and Polymerase Chain Reaction (PCR) (20.83%). The therapeutic management used included 3 combinations of antibiotics in 7 cases (31.81%), combination therapy of 2 antibiotics and an antiparasitic in 3 cases (13.63%), and combination therapy of 1 antibiotic and antiparasitic in 3 cases (13.63%). **Conclusion:** Antiparasitic therapy that can be used is imidocarb dipropionate, which works by inhibiting inositol in the erythrocytes infected with *Babesia spp.* and diminazene aceturate, which works by disrupting parasite DNA synthesis.

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## ABSTRAK

**Latar Belakang:** Babesiosis merupakan penyakit menular infeksius yang disebabkan oleh *Babesia spp.* dengan vektor caplak *Rhipicephalus sanguineus* and *Dermacentor margniatus* (tick borne disease). Transmisi babesiosis terjadi melalui gigitan caplak atau transfuse darah. Teknik diagnosis dapat dilakukan dengan pemeriksaan mikroskopis ulas darah, hematologi, kimia darah, da analisisi laboratorium PCR. **Tujuan:** Untuk mengetahui proporsisi terkait gejala klinis, peneguhan diagnosa, dan terapi yang diguanakan dari kondisi babesiosis pada anjing. **Metode:** Analisa dilakukan pada 22 lieratur kasus babesiosis pada anjing dengan periode penerbitan 2013-2023. Analisis dilakukan dengan metode analisis deskriptif adalah suatu prosedur pemecahan masalah yang menggambarkan keadaan subjek atau objek berdasarkan fakta-fakta, sifat-sifat, serta hubungan antar fenomena yang diselidiki. Metode penelitian kualitatif digunakan untuk meneliti pada kondisi objek yang alamiah, sebagai instrumen kunci, pengambilan sampel sumber data dilakukan secara purposive, teknik pengumpulan data dengan gabungan, analisis data bersifat induktif atau kualitatif, dan hasil penelitian kualitatif lebih menekankan makna. **Hasil:** Pasien anjing dengan kasus babesiosis memiliki gejala klinis tertinggi yaitu anorexia (62.5%), vomit (33.3%), pyrexia (54.16%) letargi (45.83%), urinasi berwarna kecoklatan (29.16%), dan infestasi ektoparasit (29.16%). Peneguhan diagnosa yang dilakukan diantaranya pemeriksaan mikroskopis ulas darah (100%), hematologic (91,66%), kimia darah (41,66%), dan *Polymerase Chain Reaction* (PCR) (20,83%). Manajemen terapi yang digunakan diantaranya yaitu 3 kombinasi antibiotik pada 7 kasus (31,81%), terapi kombinasi 2 antibiotik dan antiparasit pada 3 kasus (13,63%), dan terapi kombinasi 1 antibiotik dan antiparasit pada 3 kasus (13,63%). **Kesimpulan:** Terapi antiparasit yang dapat digunakan yaitu imidocarb dipropionate yang bekerja dengan menginhibisi inositol ke dalam eritrosit terinfeksi *Babesia spp.* dan diminazene aceturate yang bekerja dengan mengganggu sintesis DNA parasite.

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**Kata kunci:** Anjing; Babesiosis; Diagnosis; Terapi

## INTRODUCTION

Diseases caused by of the protozoan infectious agent *Babesia sp.* infestation are referred to as either babesiosis or piroplasmosis, and they have high morbidity and mortality rates in infected animals (Septianingsih *et al.,* 2021). *Rhipicephalus sanguineus* and *Dermacentor marginatus* are ticks that act as vectors of babesiosis. This happens because the saliva of ticks containing *Babesia spp.* sporozoites will be swallowed by dogs when the tick sucks their blood (Paramita and Widyastuti, 2019). In dogs, the large form of *Babesia spp.* can be represented by *Babesia canis* (intraerythrocytic merozoites measuring 3-5 µm or half the diameter of erythrocytes), while the small form is defined by *Babesia gibsoni, Babesia conradae,* and *Babesia vulpes* (merozoites measuring 1-3 µm or less than half the diameter of erythrocytes (Karasova *et al.,* 2022).

The clinical symptoms of babesiosis cases in dogs vary and are not specific, such as lethargy, splenomegaly, pyrexia, and decreased appetite. Pale mucosal and conjunctival colour is a common condition and is most often found in dogs due to anemia. Acute to chronic conditions are indicated by a fever that increases and decreases and anorexia (Weese and Evason, 2020). The transmission of babesiosis commonly occurs through tick bites and blood transfusions from infected dogs (Phipps *et al.,* 2016).

Tick infection is involved in the transmission of babesiosis. Sporozoites come out of the tick's salivary glands when feeding and the tick enters the blood vessels of the vertebrate host. The tick will attach and enter the erythrocytes through the endocytosis process. In the erythrocytes, the infectious agent will undergo asexual reproduction (merogony) and the daughter cells will infect new erythrocytes. Other new ticks will eat the infected erythrocytes. The transformation of merozoites into gametocytes is not known to occur in the host or the vector. In intestinal ticks, sexual reproduction occurs when gametocytes fuse to form a zygote. The zygote will infect the tick's intestinal epithelial cells and produce ookinetes that will leave the epithelial cells, before infecting the salivary glands or ovaries (transstadial or transovarial transmission). Before transmission occurs, asexual reproduction occurs in the salivary glands to become sporogony (Sykes, 2023).

Diagnostic approaches to identify babesiosis disease include examining the dog's parental history and travel history, regional epidemiological data, a history of splenectomy or blood transfusion, and a history of being bitten by other dogs. Diagnostic techniques that can be used include microscopic examination using blood smear techniques, PCR laboratory analysis, and quantitative serological tests of the protozoa *Babesia spp.* (ELISA) (Karasova *et al.,* 2022). Cases of babesiosis in dogs as pets are often found to be fairly common and involve different conditions, making it important to conduct a literature review. The purpose of the literature review of babesiosis cases in dogs is to determine the proportions related to clinical symptoms, confirmation of diagnosis, and the different therapies given.

## MATERIALS and METHOD

The study used a descriptive analysis method, which is a problem-solving procedure that describes the condition of the subject or object based on the facts, characteristics, and relationships of and between the phenomena being investigated. This study also used a qualitative research method, which is a research method used to research the natural conditions of objects, where the researcher is the key instrument, data source sampling is carried out purposively, data collection techniques are combined, and the data analysis is inductive or qualitative. Qualitative research results emphasize meaning rather than generalization. The primary data used in this study is the previous literature on cases of babesiosis in dogs for the 2013-2023 publication period including the analysis of clinical symptoms associated with a confirmation of diagnosis, and therapy management.

### Signals and Anamnesis

In 22 cases of babesiosis, only 2 of the 22 cases explained dog maintenance, which was in cages (Bhojne *et al.,* 2013) and houses (Dwi *et al.,* 2018). Signals regarding dog breeds in 24 cases included Labrador Retriever (29%), German Shepherd (9%), local (9%), and Pomeranian (9%). Signals regarding dog gender showed a percentage for males (76%), and one for females (28%). Dog categories based on age according to Harvey (2021) are 0-6 months (puppies), 6 months - 1 year (juvenile), 1-2 years (young adults), 2-6 years (mature adults), and more than 7 years (senior). The dog age with the highest percentage is mature adults (40.9).

The clinical symptoms shown in the 22 cases of babesiosis in dogs are divided into 9 systems, namely cardiovascular, metabolic, respiratory, urinary, digestive, integumentary, lymphatic, neurological, and sensory. Symptoms that appear in the cardiovascular system are pale mucous membranes (62.5%) and mucous membrane congestion (4.16%). Symptoms that appear in the metabolic system are lethargy (45.83%), panting (4.16%), dehydration (25%), jaundice (20.83%), stress (20.83%), hypothermia (4.16%), and pyrexia (54.16%). Symptoms that appear in the respiratory system are abdominal respiration (4.16%) and tussis (4.16%). Symptoms that appear in the urinary system are hematuria (20.83%), brownish urine (29.16%), oliguria (4.16%), and polydipsia (4.16%). Symptoms that appear in the digestive system are anorexia (62.5%), not drinking (4.16%), dyspepsia (4.16%), vomiting (33.3%), diarrhea (16.6%), and gastroenteritis (8.3%). Symptoms that appear in the integumentary system are dull hair (20.83%), and ectoparasite infestation (29.16%). Symptoms that appear in the lymphatic system are enlarged lymph nodes (8.3%), splenomegaly (8.3%) and lymphadenopathy (4.16%). Symptoms that appear in the neurological system are ataxia (4.16%), seizure (4.16%), and paraplegia (4.16%). Symptoms that appear in the sensory system are bilateral epiphora (4.16%).

### Supporting Examination

The supporting examinations in the 22 cases of babesiosis as a confirmation of the diagnosis include the microscopic examination of blood smears (100%), hematology (91.66%), blood

chemistry (41.66%), and Polymerase Chain Reaction (PCR) (20.83%). The results of the blood smear examination showed positive results for the formation of *Babesia sp.,* namely 9 cases of *Babesia gibsoni* (37.5%), 8 cases of *Babesia canis* (33.33%), and 6 cases of *Babesia spp.* that have not been identified (25%). The hematology examination was performed to examine any abnormalities that occurred, which included anemia (79.16%), leukocytosis (33.33%), neutrophilia (25%), lymphocytosis (25%), leukopenia (20.83%), eosinophilia (20.83%), neutropenia (4.16%), lymphocytopenia (4.16%), and monocytosis (4.16%). Blood chemistry examination showed abnormalities including hyperbilirubinemia (25%), increased BUN and creatinine (20.83%), increased ALT and AST (20.83%), hypoproteinemia (12.5%), hypoglycemia (12.5%), hypoalbumin (8.3%), increased ALT (8.3%), and increased ALP (4.16%). The examination obtained in 5 cases using Polymerase Chain Reaction (PCR) obtained positive results for *Babesia spp.*

## Theraphy

Combination therapy of 3 antibiotics (Clindamycin, Metronidazole, Doxycycline) was used in 7 cases or 31.81% (Alsaad *et al.,* 2021, Swamy *et al.,* 2019, Sharma *et al.,* 2016, Nandini *et al.,* 2016, Tauvani, 2019, An *et al.,* 2019, Islam *et al.,* 2019). A combination therapy of 3 antibiotics and an antiparasitic (Doxycycline, Enrofloxacin, Metronidazole, and Diminazene aceturate) was used in 1 case or 4.5% (Gonde *et al.,* 2016). Combination therapy of 2 antibiotics and an antiparasitic was used for 3 cases or 18.18%, namely Oxytetracycline, Doxycycline PO, Diminazene aceturate used by 1 case or 4.5% (Bhojne et al., 2013), Metronidazole, Clindamycin, and Diminazene aceturate by 1 case (Adaszek *et al.,* 2018), and Doxycycline, Metronidazole, and Imidocarb dipropionate by 1 case (Bahadur *et al.,* 2018). Combination therapy of antibiotics and an antiparasitic was used in 5 cases or 22.72%, namely Imidocarb dipropionate and Doxycycline (Pawelczyk *et al.,* 2022), Imidocarb dipropionate and Clindamycin by 1 case (Ivanescu *et al.,* 2023), Diminazene aceturate and Ciprofloxacin by 1 case (Fathipour *et al.,* 2021), and Diminazene aceturate and Chloramphenicol by 1 case (Tresamol *et al.,* 2013). Combination therapy of an anti-parasitic and causative therapy (Diminazene aceturate, Meloxicam, Neurobion) was found in 1 case or 4.5% (Sivajothi *et al.,* 2014). Combination therapy of an anti-parasitic and supportive therapy (Diminazene Aceturate and Haematinics) was done by 1 case or 4.5% (Yogeshpriuya *et al.,* 2014). Combination therapy of antibiotics and symptomatic therapy (Ceftriaxone, Dextrose, B-complex, and Iron dextran) was done by 1 case or 4.5% (Ubah *et al.,* 2019). Single antiparasitic therapy (Imidocarb dipropionate) was done by 2 cases or 9.09% (Adaszek *et al.,* 2016).

## DISCUSSION

Research by Mahalingaiah *et al.,* (2017) explains that the highest incidence of babesiosis is experienced by the Labrador Retriever breed. This is also supported by the research by Shinde *et al.,* (2021), which shows the highest incidence of the Labrador breed (11/31 cases). There is no specific reason explaining the highest incidence being in the Labrador Retriever breed (Karasova *et al.,* 2022). For the gender of the dogs experiencing babesiosis, the highest number was for males with a percentage of 76%. Research by Oguche *et al.,* (2020) explains that the gender of the animal influences the occurrence of parasitic infections through vectors, which can be impacted by the temperament and hormonal status of male dogs which may limit the attention and care given by the owner to the dog (Obeta *et al.,* 2020). Babesiosis cases based on age found that mature adults had it most commonly, which is supported by previous research (Salem and Farag, 2014). Research by Miranda *et al.,* (2022) also explained that the highest level of Babesiosis infection was experienced in dogs aged 2-4 years, caused by a poor hormonal response and maternal antibody protection which influenced the low incidence rate in younger patients.

Karasova *et al.,* (2022) also explained that the incubation period from the initial infection of the pathogenic agent and the appearance of initial clinical signs in the host was based on the number of parasites that entered the host's body. This has a time variation between 7 to 21 days. The digestive and metabolic systems showed the highest percentage of clinical symptoms, namely anorexia, vomiting, pyrexia, and lethargy. ESCCAP (2012) explained that the clinical symptoms shown in dogs infected with *Babesia canis* can occur acutely and chronically. Acute babesiosis due to *Babesia canis* is characterized by an incubation period of 1-3 weeks and the clinical symptoms shown are moderate to severe. The severity of anemia caused by erythrocyte damage is low (hematocrit <0.15-0.30 L/L) to severe (hematocrit <0.5 L/L). Other clinical signs that are also seen are erythrophagocytosis by the lymph and liver organs, and complement-mediated erythrocyte destruction (Koster *et al.,* 2015). The clinical symptoms shown in the digestive and metabolic systems are infestations of tissue hypoxia after anemia and systemic inflammatory response syndrome due to the release of cytokines in babesiosis cases (Sudhakara Reddy *et al.,* 2016).

The urinary system showed the highest percentages for brownish urine with positive blood results (hematuria) in the urine and negative continued in the bilirubin test. The bilirubin test was positive which means the patient was experiencing bilirubinuria (Hartmann *et al.,* 2019). Increased bilirubin in the urine will form a darker urine color or brownish urine. This condition can also be caused by disorders of the hepatocytes or a biliary obstruction (Meddison *et al.,* 2022).

The inflammatory response as a clinical symptom that is often found in babesiosis infection is a major aspect of the pathophysiology of babesiosis in dogs. Cytokines are responsible for mediating and regulating all immune responses to infection, thus having an important role in inducing systemic inflammation (Karasova *et al.,* 2022). Solano-Gallego *et al.,* (2016) explained that blood smears are a diagnostic method that is easy for veterinarians to perform, with a lower sensitivity than molecular diagnostic methods. A blood smear examination was carried out to see the form of the trophozoites in the blood. Blood test results where there are more than 40%

erythrocytes can indicate that the animal is experiencing babesiosis (Bhojne *et al.,* 2013). Anemia is a condition in which there is a decrease in erythrocyte and hemoglobin values, or one of them. Anemia is generally caused by bleeding, hemolysis, and bone marrow failure to produce blood cells. Failure of the bone marrow to produce blood cells can be caused by a deficiency of iron, copper, or other blood components. Anemia in babesiosis is caused by a deficiency of iron used in the erythrocyte maturation process. Hemolytic anemia also occurs due to increased reticulocytes in the blood circulation as a response to the spinal cord in hemolysis conditions (Rumlakak *et al.,* 2018). The anemia conditions that are most often found are intravascular and extravascular hemolysis. Extracellular hemolysis can be caused by splenic and hepatic phagocytes, while intravascular hemolysis is the result of the parasite life cycle (merogony phase) and immune-mediated lysis of erythrocytes (Meddison *et al.,* 2022).

Increased leukocytes occur as body defense cells that are distributed throughout the body to protect against various invasions of microorganisms and foreign objects (Muzaky *et al.*, 2021). Secondary babesiosis infection caused by the entry of bacteria from tick bite wounds causes a response of allergen agents and eosinophilia. This is the body fighting parasitic infection (Paramita and Widyastuti, 2019). Weese and Evason (2020), explained that dogs infected with *Babesia sp.* generally show thrombocytopenia. Increased bilirubin levels and ALT activity are signs of stress in the liver caused by the release of cytokines as inflammatory mediators or hypoxic conditions that cause liver disorders (Gonde *et al.,* 2016). Increased AST and ALT result in increased enzymes from liver parenchymal cells that experience obstruction, necrosis, or changes in membrane permeability, indicating liver dysfunction. Hyperbilirubinemia occurs in hemolysis (Bilawal *et al.,* 2017). More severe increases will be indicated by an increase in BUN and creatinine in Babesiosis cases. Kidney disorders are caused by damage to the nephron cells due to refractory hypotension, thereby reducing renal tissue perfusion or the renal filtration rate (Patwary *et al.,* 2022). PCR testing is a test to determine and evaluate whole blood or spleen aspiration, which is the most sensitive and specific for diagnosing active infection. However, results and sensitivity vary between *Babesia spp.* species. Serial testing of the samples 2-4 times with an interval of several weeks can increase sensitivity in chronic infections (Weese and Evason, 2020).

Therapeutic management is carried out using a combination of antibiotics and anti-parasitics. Doxycycline is a first-class tetracycline antibiotic that works as a bacteriostatic by reversibly inhibiting 30s ribosome synthesis and preventing the relationship of aminoacyl-tRNA with other bacterial ribosomes. Further inhibition of protein synthesis happens in the mitochondria by binding to 70s ribosomes (Holmes and Charles, 2009). Doxycycline has high lipophilicity properties, so doxycycline can enter the erythrocytes to inhibit the development of intraerythrocytic protozoa (Deshmuk *et al.,* 2009). Azithromycin is a macrolide antibiotic that works bacteriostatically, namely inhibiting protein synthesis by penetrating the cell wall and binding to the 50s ribosome subunit. Clindamycin is a lincomycin antibiotic that works bacteriostatically or as a bactericidal by binding to the 50s ribosome subunit, inhibiting the formation of peptide bonds. Metronidazole is a class of nitroimidazole antibiotics that have a bactericidal mechanism of action by inhibiting the synthesis of DNA and nucleic acid proteins (Plumb, 2011). Clindamycin, metronidazole, and doxycycline are combinations of antibiotics that are used and have been proven to be effective for Babesiosis therapy in dogs. Other antibiotic combinations that can be used are doxycycline, enrofloxacin, and metronidazole, which have the same effectiveness.

Parasite treatment using imidocarb dipropionate is recommended by intramuscular and subcutaneous administration routes with repeated doses within 2 weeks. The mechanism of action of the drug is by blocking the entry of inositol into erythrocytes that have *Babesia spp*. in them, causing the parasite to starve, disrupting reproduction, damaging the nucleic acids, and inhibiting cell repair or replication. Side effects of the treatment include pain during injection and cholinergic effects that can be reduced by administering Atropine sulfate premedication (Vishwakarma and Nandi, 2020). Diminazene aceturate works by interfering with parasite DNA synthesis and aerobic glycolysis, and is excreted through the kidneys and liver. This drug is good for use in Abesia gibsoni infections but is more effective in large *Babesia spp.* (Karasova *et al.,* 2020).

## CONCLUSION

The most common clinical symptom for dogs infected with babesiosis is anorexia (62.5%). Confirmation of the diagnosis is done through a blood test (100%). The therapeutic management used includes a combination of 3 antibiotics in 7 cases (31.81%). The antibiotics used are antibiotics that have the ability to penetrate cell walls and bind ribosomal subunits. The anti-parasitic therapies that can be used include Imidocarb dipropionate, which works by inhibiting inositol in the infected erythrocytes, and Diminazene aceturate, which works by disrupting parasite DNA synthesis.

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## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## AUTHOR'S CONTRIBUTION

Conceptualization: ADN, DP, TW, AN, Writing-original draft preparation: ADN, Writing-review editing: ADN, DP, TW, AN.

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