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Overview of canine babesiosis with special emphasis on N-acetylcysteine and coenzyme Q10 as an adjunct therapy for its management

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Abstract
Canine babesiosis is a tick-borne disease caused by the parasite of the genus *Babesia.* It is mainly transmitted by ticks. The major complications. Of babesiosis in dogs are hepatic failure, kidney failure, DIC, oxidative damage to red blood cells, and immune-mediated hemolyticanemia. Oxidative stress can cause lipid peroxidation and erythrocyte injury in affected dogs. Clinical symptoms are usually associated with hemolysis caused by the organisms in the erythrocytes; however, anemia may also be accompanied by an inflammatory response or an immune-mediated component. In this review, we discuss the clinical signs, clinical biomarkers, diagnosis, and treatment of the disease with specific therapy along with the use of antioxidants like N-acetyl cysteine and Coenzyme Q10 for the therapeutic management of babesiosis in dogs.

Keywords: Antioxidant, Babesiosis, Coenzyme Q10, N-acetylcysteine

Introduction
Tick-borne diseases are scattered worldwide (FAO, 2004) and are the major hindrance to the livestock industry as well as companion animal health care, mainly in subtropical and tropical regions and even in temperate climate regions (Irwinand Jefferies, 2004) [45]. Due to the large population of stray dogs in India, they transmit many hemoprotozoal diseases and act asmaintenance hosts for some tick-borne organisms (Azaziah *et al*., 2010) [7]. Babesiosis is a hemoprotozoal disease caused by parasites of the genus Babesia, order Piroplasmida, phylum Apicomplexa *B. gibsoni, B. vogeli,* and *B. rossi*are identified. Babesiosis in dogs is a tick-borne disease caused by *Babesia canis,* a large piroplasm, and *Babesia gibsoni*, a small piroplasm. These infect the RBCs (red blood cells) of dogs and typically cause hemolyticanemia. Most dogs with babesiosis develop hemolyticanemia or thrombocytopenia, varying degrees. Of anorexia, fever, splenomegaly, and icterus. The pathogenicity of Babesia is also known to differ in different parts of India which might be due to strain and species variation *B. gibsoni*is the most prevalent of small Babesia and is endemic in Asia. It is transmitted by *Rhipicephalus sanguineus, Haemaphysalislongicornis.* And other species of Rhipicephalus (3 host ticks), *Dermacentor* (Casapulla *et al*., 1998) [18]. The major complications of babesiosis in dogs are hepatic failure, kidney failure, DIC (disseminated intravascular coagulation), oxidative damage to red blood cells, acute pancreatitis, Immune-mediated hemolyticanemia, and pulmonaryedema (Jacobson., 1996) [47]. Complete blood count, serum biochemical examination, urine analysis, abdominal radiography, or ultrasonography are being considered for screening of the *Babesia* organism (Varshney *et al*., 2002) [80]. Platelet destruction by immune-mediated reactions, splenic sequestration, and excessive consumption due to mild vasculitis, or bone marrow failure are the most common cause of thrombocytopenia in dogs affected with *Babesia gibsoni* infection. Diagnosis of *Babesia gibsoni* is mostly done conventionally by Giemsa, Wright, or Diff-Quickstaining of a blood smear from peripheral blood. Recent advanced molecular techniques like polymerase chain reaction (PCR) have greater sensitivity and specificity to detect and identify piroplasm

than conventional methods (Ionita *et al*., 2012) [44].
Newer treatment includes the combination of clindamycin, metronidazole, and doxycycline (Suzuki *et al*., 2007) [72] and atovaquone with azithromycin having good efficacy and safety (Birkenheur., 2014) [10]. Specific therapy fails to stimulate bone marrow which is required to overcome evolved pancytopenia. Antiprotozoal drugs do not prevent the oxidative stress on erythrocytes caused by the multiplication of *Babesia gibsoni*. Cardiac disorder and oxidative stress in canine babesiosis are less explored in terms of disease pathogenesis. Therefore, a systematic study of the pathogenesis of the disease, and its early and accurate diagnosis with newer therapy may be undertake into overcome all these disease complications.

Canine babesiosis
Canine Babesia is mainly classified into small and large forms. Three main species of large. Babesia that infect dogs are *B. vogeli, Babesia canis, and Babesia rossi.* These three species of *Babesia* are antigenically distinct are transmitted by different vectors and differ in pathogenicity and geography distribution (Uilenberg *et al*., 1989) [79]. The large form of Babesiasp in canines is *Babesia canis* having a size of 3 micrometres to 5 micrometres. *Babesia gibsoni* is a small organism, measuring from 1 to 3.2 micro-meters in size, and is pleomorphic. More virulentsub species of *Babesia gibsoni* has been recently identified in California (Kjemtrup *et al*., 2006) [49].

Transmission
Different types of ticks like *Rhipicephalus sanguineus*, *Dermacentor* species, and *Haemaphysalisellipticum*, can transmit various forms of Babesia to dogs. *Babesia gibsoni* is transmitted by *Haemaphysalislongicornis* and *H. bispinosa*, while *B. annaeis*is spread by *Ixodes hexagonus* (Lobetti, 2006) [56]. Transmission of infection can occur through both transovarial and transstadial routes, with ticks able to carry the infection for several generations. Babesia organisms multiply in dogs through multiple fission, generating merozoites. Ticks become infected after consuming parasitized host red blood cells. Within the tick, merozoites undergo a complexity in their life cycle, including multiple fissions that lead to the production of sporozoites in the arthropod's salivary glands. These sporozoites are then released into a host's circulatory system through tick saliva. Transmission of Babesia species can also happen through blood transfusion, and there is suggestive evidence that *B. gibsoni* can be transmitted through dog bites (Birkenheur *et al*., 2014) [10]. Additionally, recent research has confirmed transplacental transmission from mother to off spring as another mode of Babesia transmission in canines (Fukumoto *et al*., 2005) [36].

Pathogenesis
Babesia species can affect dogs of all age groups. The incubation period for Babesiosis varies, ranging from 14 to 28 days for *B. gibsoni* and 10 to 21 days for the *Babesia canis.* Female ticks usually feed on their host for about a week and then leave before the disease manifests. Upon infection, the host generates an immune reaction influenced by various factors. The antigen of the parasite on the infected RBC membranes triggers the production of antibodies, opsonisation, and removal of infected red blood cells by mononuclear phagocytic cells in the haemolymphatic system (Taboada and Lobetti, 2006) [74].
Survivors of babesiosis may become chronic carriers without displaying clinical signs, as the immune system struggles to eradicate the infection. The severity of a disease mainly depends on the species of Babesia, the dog's age, concurrent infections, and the host's immune status. The disease presentation can vary from the per acute to acute, chronic, or even subclinical forms. A highly virulent species, *Babesia rossi* is predominantly found in South Africa and often causes peracute-to-acute disease.

Clinical Signs
Babesiosis in Canines can be classified as complicated or uncomplicated (Ayooband Prittie, 2010) [3]. Clinical signs in uncomplicated babesiosis include depression, anorexia, weakness, pale mucous membranes, tachycardia, tachypnoea, splenomegaly, and fever. Clinical signs in complicated cases of Babesia are hepatic, cardiovascular, hemolyticanemia, respiratory, renal, coagulopathic dysfunction, gastrointestinal, and neurologic. It is believed that clinical signs are the outcome of tissue hypoxia. Following the anemia and a concomitant systemic inflammatory response syndrome (SIRS) caused by the marked cytokine release (Lobetti, 2006) [56]. The pathogenesis of the anemia is incompletely understood, both intravascular and extravascular hemolysistake place but other mechanisms like poor bone marrow response are thought to play a role. Anaemia is the predominant clinical sign and results in both intravascular. And extravascular hemolysis. Parasitic activity directly damages the erythrocyte cell membrane, resulting in increased osmotic fragility and subsequent intravascular hemolysis. *B. gibsoni* infection. May follow hyper-acute, acute, or chronic course. The acute course is most common and is characterized by lethargy, fever, lymphadenopathy, hemolyticanemia, thrombocytopenia, and splenomegaly (Conrad *et al*., 1991) [22]. The hyper-acute state is rare and is characterized by shock and extensive tissue damage.
Thrombocytopenia can occur in combination with other hematologic abnormalities or as a singular entity, and may be transient or persistent (Tuttle *et al*., 2003) [78]. It is commonly seen in both *B. canis* subsp. *rossi*and *B. gibsoni* infection and is the most consistently reported hemostatic abnormality (Taboada and Lobetti, 2006) [74]. Coagulopathic consumption in association with DIC is postulated. Splenic platelet sequestration, immune-mediated platelet destruction, or both may be contributory. Icterus and elevated hepatic enzymes occur frequently. Although the associated hemolyticanemia contributes to hyperbilirubinemia, it is not the sole cause. Welzl *et al*. (2001) [81] studied systemic inflammatory response syndrome and multiple organ dysfunction syndromes (MODS) in dogs with complicated babesiosis, and to assess their impact on the outcome.

Organ Involvement in Babesiosis
Anaemia is the predominant. Clinical syndrome and development of this anemia is multifactorial which results in both intravascular and extravascular hemolysis. Babesia parasite directly damages the cell membrane of erythrocytes result in increased osmotic fragility and intravascular hemolysis. Immune-mediated hemolytic anaemia (IMHA) may occur secondary to the inappropriate production of anti-erythrocyte membrane antibodies and is assumed to occur with all the Babesia spp. Elevated concentrations of anti-erythrocyte membrane antibodies and erythrocyte-bound IgG; immunoglobulin G have been documented in dogs. Infected with *Babesia gibsoni* (Adachi and Makimura., 1992) [2].

Continued hemolysis, despite appropriate anti-babesial therapy, is the most prominent feature of this. Complication. Diagnosis requires demonstration of saline agglutination of RBCs spherocytosisor both (Taboada and Lobetti, 2006) [74]. A positive Coomb test is not considered a reliable tool for the diagnosis of IMHA in Babesiosis as 84% of canine patients infected with *Babesia canis* or *Babesia gibsoni* have positive Coombs tests (Farwell *et al*., 1982) [31].

Oxidative stress can cause lipid peroxidation and erythrocyte injury, with resultant methemoglobinemia, Methemoglobinuria, as well as elevated methemoglobin to total hemoglobin ratios, which have been documented in Babesia-infected dogs (Lobetti and Reyers., 1996) [47]. Increased macrophage production of 10 superoxide and other reactive oxygen species has been demonstrated in *Babesia gibsoni* infected dogs (Otsuka *et al*., 2002) [64]. Studies of experimentally induced *Babesia gibsoni* infection suggest that free radical-initiated oxidative stress to the red blood cells is necessary for anti-erythrocyte membrane antibody production (Morita *et al*., 1993) [33]. Furthermore, erythrocyte oxidation may enhance susceptibility to macrophage-mediated bone marrow phagocytosis (Otsuka *et al*., 2002) [64].

Multiple Organ Dysfunction Syndrome can occur after infection with most pathogenic *Babesia* species, particularly *Babesia canis* subsp. *rossi* and *Babesia gibsoni*. The complications include disseminated intravascular coagulopathy (DIC) thrombocytopenia, red biliary syndrome, acute renal failure (ARF), hepatopathy, rhabdomyolysis, CNS dysfunction, non-cardiogenic pulmonary edema, pancreatitis, systemic hypotension, cardiac dysfunction, hypoxemia, hypoglycemia, and metabolic acidosis with hyperlactatemia (Leisewitz *et al*., 2001) [53].

Acute renal failure (ARF) appears to be an uncommon complication of babesiosis (Pages, 1992). The usual warning sign of acute renal failure (ARF) in babesiosis is anuria or oliguria despite adequate rehydration. ARF was more likely to occur in older dogs, and the prognosis was better in young, polyuric animals. The pathogenesis of ARF is multifactorial. The cause of renal hypoxia is anemia, capillary sludging, and systemic hypotension with compensatory renal vasoconstriction, immune-mediated membranoproliferative glomerulonephritis also leads to renal damage (Wozniak *et al*., 1997) [83]. Blood urea nitrogen is an unreliable indicator of renal dysfunction as the BUN measurement. Is affected by intravascular hemolysis. Serum creatinineis a useful diagnostic tool for renaldys function as it is unaffected by hemolysis. The degree of proteinuria correlates with the severity of the disease rather than the degree of renal damage (Lobetti and Jacobson., 2001) [53].

Icterus is reported to occur in advanced cases of canine babesiosis, and, if severe, may be associated with increased mortality. In the babesial infection, centrilobular hepatitis and severe histopathologic changes are noticed which results in hypoxic liver damage (Wozniak *et al*., 1997) [83]. Kupffer cell hypertrophy and an increased number of CD31 lymphocytes and macrophages have been noticed which suggests that immune-mediated inflammation plays an important role (Wozniak *et al*., 1997) [83]. Histopathological and laboratory evidence of hepatic damage are common but hepatopathy is not reported to affect the outcome (Welzl *et al*., 2001) [81].

Acute respiratory distress syndrome (ARDS) is a common complication of more pathogenic strains of Babesia species. The pathogenesis of ARDS includes a systemic inflammatory response syndrome, secondary to the production of inflammatory cytokines. And reactive oxygen species. The clinical signs include moist cough, tachypnoea, serosanguineous frothy secretions, and hypoxemia. The radiograph reveals either a diffuse or caudodorsal patchy alveolar infiltrate with normal cardiac silhouette or vessel size. In *Babesia gibsoni* infected dogs, there may be multifocal deposition of immunoglobulin Mantibodies within the walls of inflamed pulmonary arteries (Wozniak *et al*., 1997) [83]. ARDS is a catastrophic complication and is associated with a marked increase in mortality (Mahr *et al*., 2000) [59].

Cerebral babesiosis has been defined as a combination of nervous signs and characteristic pathological changes, including. Sludging of parasitized erythrocytes in small vessels in the brain (Basson, 1965) [9]. Clinical signs in dogs often have a hyperacute onset (Hase, 1947) [40]. The following signs reported in association with cerebral babesiosis are incoordination, muscle tremors, nystagmus, hind-quarter paresis, anisocoria, intermittent loss of consciousness, seizures, stupor, and coma (Wright and Goodger, 1988) [87]. The pathological changes reported most frequently in the brains of dogs with cerebral babesiosis are congestion, macroscopic and microscopic hemorrhages, and sequestration of parasitized erythrocytes in the capillary bed. Oedemais an inconsistent finding. Clinical signs resolve in some patients after antibabesial therapy and the development of neurological Signsis associated with a high mortality rate (Welzl *et al*., 2001) [81].

Acute pancreatitis is a common occurrence in canine Babesiosis (Jacobson, 1996) [47]. Pancreatitis is more commonly seen in patients who are suffering from MODS and is associated with an 18% increase in mortality (Breitschwerdt *et al*., 1983) [11]. Clinical signs of pancreatitis are inappetence, vomiting, diarrhea, and abdominal pain. The pathogenesis of pancreatitis includes ischemic- reperfusion altered blood flow and oxygen delivery due to hypotensive shock, anemia and haemoconcentration, altered lipid metabolism, and pro-inflammatory cytokine production (Mahr *et al*., 2000) [59]. Rhabdomyolysis is clinically characterized by muscle tremors, pain, and pigmenturia. It is seen rarely and is usually accompanied by other complications like acute kidney injury, cerebral babesiosis, and ARDS. There is an increase in serum myoglobin, muscle necrosis, muscle enzymes, and hemorrhageduring necropsy (Jacobson and Lobetti, 1996) [47].

Cardiac dysfunction in dogs having babesiosis has traditionally been regarded as a rare complication with most lesions reported as incidental endings at the post-mortem examination. Macroscopic cardiac lesion includes pericardial effusion, and epicardial, pericardial, and endocardial hemorrhage, which usually involve one or more of the chambers with the left ventricle being most affected. Documented cardiac histopathology. Changes are necrosis, hemorrhage, inflammation, and micro-thrombi in the myocardium. Lesions may be multifocal but are limited to one area in the myocardium (Dvir *et al*., 2004) [27]. With cardiac dysfunction in dogs, there is reduced renal blood flow and glomerular filtration due to redistribution of blood which is common in the early case of heart failure (Lobetti and Jacobson., 2001) [47].

Thrombocytopenia can occur in combination with other hematologic abnormalities or as a singular entity, and it may be transient or persistent. It is most commonly seen in *Babesia gibsoni* and *Babesia canis* subsp. *rossi* infection and is the most consistent reported hemostatic abnormality (Taboada and Lobetti., 2006) [74].

Coagulation derangement, also known as hypercoagulability, is considered likely in several systemic diseases affecting small animals (Wiinberg *et al*., 2008) [82]. If uncontrolled, the hypercoagulable. State may lead to DIC, which has been identified as a major risk factor. For poor outcomes in both humans. And canine medicine (Laforcade *et al*., 2003) [25]. Criteria for the definition of DIC in humans established by the International Society on Thrombosis and Haemostasis include procoagulant activation, inhibitor consumption, and increased fibrinolytic activity (Wiinberg *et al*., 2008) [82]. Clinical signs associated with DICvary considerably and can range from non-overt DIC to signs of organ failure secondary to microvascular thrombosis, and overt hemorrhage (overt DIC) (Wiinberg *et al*., 2008). [82]

Diagnosis

Babesiosis should be suspected when a dog is presented with anemia or thrombocytopenia is discovered or if there is a history of tick exposure or history of the animal living in or previous history of travel to the tick-endemic area (Irwin, 2010) [45]. The diagnosis of canine babesiosis should be as specific as possible because prognosis and response to treatment are variable (Boozer and Macintire, 2005) [13].

Microscopic examination

According to Taboada and Lobetti (2006) [74], erythrocytes must be shown to contain organisms to provide a conclusive diagnosis of Babesia infections. A useful diagnostic technique for acute infections with moderate or high parasitaemia is the light microscopic examination of blood smears. Because parasitized erythrocytes tend to sludge in the capillaries, evaluating smears made from peripheral blood, such as the nail bed or tip of the ear, increases the chance of finding the parasite (Abdullahi *et al*., 1990) [1].

Molecular Diagnosis

The most sensitive method for diagnosing Babesia infections is genetic-based testing, particularly PCR testing (Taboada and Lobetti, 2006) [74]. Fukumoto *et al*. (2005) [36] noted that PCR targets parasitic DNA rather than anti-Babesia antibodies, making it a reliable diagnostic tool for peracute, acute, and chronic infections in young dogs and immunocompromised patients. Lin and Huang (2010) reported that some cases of subclinical *B. gibsoni* infection may go undetected solely by microscopic examination, emphasizing the importance of PCR assays to identify carriers. PCR testing allows for species-specific amplification of regions of parasite DNA, providing a definitive diagnosis. It is particularly valuable for detecting low levels of parasitemia, identifying subclinical infections, and monitoring the response to therapy (Boozer and Macintire, 2005) [13]. Recently, several PCR methods have been developed to diagnose *Babesia* infection with high sensitivity and specificity (Inokuma *et al*., 2004) [43].

Treatment

The removal of the parasite and the correction of the potentially fatal anemia are the main objectives for treating canine babesiosis. There have been notable advancements in the kinds and accessibility of therapies for canine babesiosis. Therapy should be begun early and is frequently administered empirically on clinical suspicion in highly endemic areas or breeds with elevated infection risk.

The immune system does not eliminate the infection after the first parasitemia and continues to be the chronic carrier of the illness. Relapses can happen months or years after the initial incident, and long-term effects such as polyarthritis or glomerulonephritis may manifest. No medications, including diminazene aceturate and imidocarb diproprionatehave been shown to effectively treat *Babesia gibsoni* infections in dogs. For Babesia canis infections, diminazene aceturate at doses of 3.5 to 5 mg/kg is frequently beneficial. On the other hand, *B. gibsoni* infections should be treated with doses of 7.5 to 10 mg/kg (Taboada and Lobetti, 2006) [74]. Recent successful treatment modalities have shown promising results in the cure of *Babesia gibsoni* infection in dogs. These include a combination of clindamycin at the dose rate 25 mg/kg every 12 hours orally, metronidazole at the dose rate 15 mg/kg every 12 hours orally, and doxycycline at the rate of 5 mg/kg body weight every 12 hours orally (Suzuki *et al*., 2007) [72], as well as azithromycin at the dose rate of 10 mg/kg body weight every 24 hours orally with atovaquone (13.3 mg/kg body weight orally every 8 hours for 10 days), which demonstrated good efficacy and safety. Clindamycin alone (25 mg/kg body weight orally every 12 hours for 1-3 weeks) can also be effective if other antibabesial drugs are not available (Jadhav *et al*., 2011) [48].

Clinical biomarkers

Haematology

As *Babesia gibsoni* is a hemoprotozoal disease, a complete blood count to check for anemia and blood cell abnormalities should be done (Wozniak *et al*., 1997; Casapulla *et al*., 1998) [83, 18]. Brahma *et al*. (2019) [14] studied molecular examination and hematobiochemical changes in canine babesiosis infected dogs. In this study, 8 cases infected with Babesia were confirmed through hematological, biochemical, and multiplex PCR. The most common clinical signs in dogs were anorexia, pale or icteric mucous membranes, high rise of temperature, and dark urine color. The hematological parameters showed decreased levels of RBC, Hemoglobin, PCV, and platelet levels.

Biochemical parameters

Alanine aminotransferase (ALT)

Serum ALT activity sharply increases. Within 24-48 hr up to 100 times normal or higher to peak five days after injury and a marked increase in serum ALT activity develops in association with haemoprotozoan diseases (Hoe and Jabara., 1967). Ongoing hepato-cellular damage. Is characterized by consistent elevated (ALT) serum alanine aminotransferase activity.

Total protein and albumin

Tiwari *et al*. (2001) [76] recorded low levels of serum protein. And albumin in haemoprotozoal infection. As hepatic function. Declines coincide with a decline in albumin levels. Sterczer *et al*. (2001) [71] observed hypoalbuminemia in an advanced state of haem protozoan disease. The decrease. In albumin and an increase in globulin leads to a decrease in albumin: globulin ratio.

BUN and Creatinine

Elevated serum urea alone is an. unreliable indicator of renal insufficiency in babesiosis, as a disproportionate rise in urea (compared with creatinine) was found in over half of 93 cases evaluated (Reyers., 1992) [70]. Renal failure is diagnosed. Based on ongoing. Evaluation of urine volume, urinalysis, and degree of azotemia. Most dogs in the severe. And complicated cases. Had elevated serum urea, and creatinine

(Gossett *et al*., 1987) [37]. The serum creatinine does not mirror the serum urea level.

Disseminated intravascular coagulation (DIC)

DIC is a syndrome caused by the systemic generation of thrombin. Diagnosis is made by finding abnormalities in at least 3 of 4 laboratory values, namely, platelet count, and prothrombin time. Fibrinogen and fibrinogen/fibrin degradation products. In haemoprotozoan diseases, platelet count decreases and prothrombin time is prolonged. Most hyperfibrinolysis is caused by a high offense factor or a low defensefactor. DIC is divided into two stages. One is overt-DIC and the other is non-overt-DIC. At present, organ failure. Due to hypercoagulabilityis an important aspect of pathology of DIC.

Cardiac biomarkers

Dog babesiosis has been linked to cardiac disease (Dvir *et al*., 2004) [27], yet the diagnosis is clinically challenging. Acute respiratory distress syndrome, severe anemia, and dyspnea are symptoms that are like acute heart failure. The most frequent ones are micro-infarction and inflammation of the heart in babesiosis-affected dogs. Canine babesiosis has been linked to hypotension (Jacobson *et al*., 2000) [47]. The presence and intensity of hypotension are related to the severity of the disease and are brought on by cardiac pathology. Cardiac troponin and natriuretic peptides are examples of blood-based chemicals linked to cardiac damage, anatomy, and functionality. Myocyte damage results in the release of troponins or natriuretic peptides which are liberated from cardiac tissue in reaction to stress on the heart wall (Oyama *et al*., 2007) [65].

Cardiac Troponin

Troponins are a sensitive and persistent indicator of heart damage. A very specific and sensitive marker of myocardial damage is cardiac troponin-I which is detectable by immunoassay techniques in plasma. Prior research on babesiosis in dogs has demonstrated heart injury, altered ECG patterns, and elevated cardiac troponin-I (Lobetti *et al*., 2006) [56]. In one investigation, dogs infected with Babesia displayed a histological cardiac lesion and had higher cTnI concentrations (Dvir *et al*., 2004) [27]. According to Rossi *et al*. (1999), the release of cardiac troponin is also observed in liver disorders, significant skeletal muscle, and chronic renal failure. This is a crucial factor to consider while dealing with canine babesiosis, particularly when it's complex and involves rhabdomyolysis, liver damage, and renal failure (Jacobson *et al*., 1996) [47].

NT pro-BNP assay

It has been shown that natriuretic peptides are present in cases of severe heart disease (Boswood *et al*., 2005) [12]. The quantitative markers of ventricular wall stress with the highest specificity and sensitivity for cardiac stress are NT-proBNP and brain natriuretic peptides (Chen *et al*., 2009) [20]. In ventricular myocytes, pre-prohormone BNP is produced and transformed into prohormone form. When the pro-BNP pro-hormone is derived from cleaves into NT-proBNP and C-BNP, two molecules are produced. To diagnose congestive heart failure, two diagnostic tools are used: NT-proBNP and C-BNP concentrations (Oyama *et al*., 2009) [65]. Due to its rapid degradation in circulation, laboratory testing is challenging for C-BNP. On the other hand, NT-proBNP has an extended half-life and is more readily detected (Oyama *et al*., 2010) [65]. Elevated plasma in veterinary medicine concentrations of NT-proBNP have caused canine babesiosis and gastrointestinal disorders, traumatic brain injuries, and neurological disturbances (Lee *et al*., 2011) [52].

Ultrasonography

Nyland and Hager (1985) [63] observed normal hepatic parenchyma with its consistent, slightly rough echotexture, the hepatic parenchyma makes the gall bladder and bigger blood arteries evident. The gall bladder has smooth, well-defined borders and is anechoic. When compared to the right kidney, the normal liver appears hyperechoic or isoechoic, rougher in echotexture, and less echogenic than the spleen. Hepatopathy, splenomegaly, and various organ failures are all associated with *Babesia gibsoni.*

According to Fraga *et al*. (2010) [34], ultrasonography can be used to diagnose, track, and treat canine babesiosis and its systemic consequences. Due to the high occurrence of this lesion in dogs with Babesia infection, diffuse heterogeneous splenomegaly on ultrasonography can support the diagnosis of Babesia infection. Splenomegaly with diffuse heterogenic parenchyma and decreased echogenicity was reported to be the most important finding in dogs with *Babesia gibsoni* infection. Diffuse hypoechoic hepatomegaly in USG and enhanced cortical echogenicity of the renal parenchyma have been found more commonly in severe uncomplicated and complex babesiosis.

Electrocardiography

Anaemia, ARDS, hypotension (Jacobson *et al*., 2000) [47], acidosis, hypokalaemia, and acute renal failure are among the systemic and metabolic illnesses that can cause ECG abnormalities in babesiosis in canines.

Both humans and dogs may experience aberrant ECG readings due to myocardial lesions linked to canine babesiosis (Charpentier *et al*., 2004) [19]. Dogs having babesiosis have been observed to exhibit first- and second-degree sinus arrest, arrhythmias, sino-atrial block, and other ventricle tachycardia, ventricular early depolarization, and AV block. Changes in the electrocardiogram include low amplitude R-waves, prolonged QRS time interval, Large T wave, ST segment deviation, and R wave notching (Dvir *et al*., 2004) [27]. R wave notching is an inconsistent result that is more frequently observed in dogs with secondary IMHA when it comes to babesiosis (Tilley, 1992) [75].

Oxidant-antioxidant system

Free reactive oxygen and nitrogen species are produced by the organism during regular metabolic activities (Dianzani *et al*., 1992) [24]. When oxidative stress happens due to a pathological state. This phenomenon causes cellular components to change, which might result in illnesses. By strengthening cellular defenses with antioxidants this can be effectively alleviated. The immediate release of oxygen and hydrogen peroxide is known as oxidative stress. The biological effects of oxidants come from a controlled balance between the system's internal cellular defense mechanisms and the generation of reactive oxygen species (Hollan, 1995) [42]. According to Moral *et al*. (1997) [61], the main enzymes found in RBC that combat harmful substances like hydrogen peroxide and superoxide radicals are SOD, catalase, and glutathione peroxidase. Reduced glutathione concentration and MDA concentration are higher in hemoprotozoal-induced oxidative stress.

Conflicts in the therapy of canine babesiosis

Eliminating the causal factor and treating the severe anemia are the primary goals of the therapy. After the initial infection, the immune system is unable to eradicate the parasitemia and

the animal develops into a chronic disease carrier. Recurrence of the infection might happen months or years later and cause polyarthritis or glomerulonephritis as a sequela. As of right present, no one can cure hemoprotozoan illnesses such as those caused by the Asian genotype of *Babesia gibsoni*, which affects canine species. Treatment for small-form babesia is typically more challenging (Boozer and Macintire, 2005) [13]. *Babesia gibsoni* has proven to be especially difficult to treat successfully (Wulansari *et al*., 2003) [88].

It is unknown whether specific cases benefit from the use of medications such as erythropoietin or granulocyte stimulating factor, which are used to stimulate bone marrow in a small number of individuals. Individuals with aplastic anemia in humans can receive a bone marrow transplant. However, this approach is not frequently employed with animals (Merrill, 1970) [60]. Although aplastic pancytopenia can be recovered, there are risks associated with doing so. The transfusion of platelets presents another major challenge in the management of thrombocytopenia. The chances of platelets surviving after transfusion are extremely low due to their extremely short lifespan. There is occasionally a risk and potential consequences associated with giving blood transfusions to dogs surpassing the benefits that can harm the recipient animal. The lifespan of blood storage is impacted by inadequate facilities and methods. Whole blood used for long-term storage may result in storage lesions. An animal receiving systemic glucocorticoid therapy is more vulnerable to secondary infections, which impair immunity (Torres *et al*., 2005) [77]. Thus, the management of canine babesiosis should concentrate more on increasing bone marrow activity in affected dogs using innovative adjunct therapy.

N- acetylcysteine (NAC)

N-acetylcysteine is a prodrug of cysteine and a precursor of glutathione that scavenges free radicals and forms complexes with metal ions (Atkuri *et al*., 2007) [6]. It is used as a sputum liquefier (inhalation) and as an antidote to acetaminophen intoxication. Additionally, it is utilized as a dietary supplement. As a hepatoprotectant, it increases the delivery of oxygen in cases of acute liver failure by either increasing vascular tone or restoring intracellular cysteine and glutathione. NAC also affects the hepatic mitochondria's energy metabolism and has anti-inflammatory properties preventing polymorphonuclear cells from adhering to endothelial surfaces and PMN-activating cytokine release (Zafarullah *et al*., 2003) [89].

When the generation of reactive oxygen species surpasses the capacity of cells to neutralize free radicals, intracellular oxidative stress takes place. By engaging with the electrophilic moiety of free radicals through its free thiol side chain, N-acetylcysteine functions as a direct antioxidant. It quickly reacts with hydroxyl nitrogen dioxide and carbon trioxide ions to eliminate free radicals generated by WBC. In addition to its direct antioxidant characteristic. Through the replenishment of intracellular GSH, the body's primary antioxidant with a variety of cellular activities, NAC also serves as an indirect antioxidant (Akca *et al*., 2005) [4].

N-acetylcysteine increases the activation of pro- and pre-B cells in the bone marrow and counteracts oxidative stress by neutralizing reactive oxygen species (Palmer *et al*., 2011) [67]. Because it maintains every blood profile parameter and stops cellular death, it offers cytoprotection to the hematopoietic cell (El-Sayed *et al*., 2010) [28]. NAC exhibits strong radioprotective properties and reduces cytotoxicity and genotoxicity as well as effects in the bone marrow of many animal species when exposed to radiation. Additionally, it promotes the long-lasting engrafting of hematopoietic stem cells, and hematopoietic progenitor cells, and improves clonogenic activities. NAC increases hemopoietic progenitor cells' potential for long-term self-renewal (Ito *et al*., 2006) [46]. Therefore, it can used as an adjunct therapy along with specific treatment for bone marrow stimulation in affected dogs.

Coenzyme Q10

First discovered in the 1950s, coenzyme Q10 (2,3-dimethyoxy-5-methyl-6-decaprenyl-1,4-benzoquinone) was identified by Festenstein *et al*. (1955) [32] and Crane *et al*. (1957) [23]. It was first discovered in the mitochondria of a cow's heart and then explained by Folkers *et al*. (1993) [33]. Coenzyme Q10 is a necessary part of the electron transport chain and is required for the synthesis of ATP. According to Greenberg *et al*. (2005) [38], CoQ10 is also said to have anti-inflammatory and free-radical-scavenging properties. It has demonstrated subtle but substantial antioxidant activity. As a result, it can effectively guard against the damaging effects of reactive oxygen species, free radicals, and toxic chemicals, shielding the body from injury (Ruiz-Jiménez *et al*., 2007) [85] by shielding proteins and membranes from oxidative reactions (Cluis., 2012) [21].

Ubiquinone is the name for its oxidized form, and ubiquinol is the name for its reduced form. Both forms coexist and are made possible by successive redox reactions function to replenish one another inside the Q cycle (Tacchino *et al*., 2019) [73]. Lipophilic antioxidants have a role in the biological activity of the essential molecule (Nelson, 2017) [62]. Produced intracellularly, ubiquinone is a strong endogenous antioxidant that participates in electron transport between complexes I or II and complex III in the mitochondrial electron transport chain (Ernster *et al*., 1995) [29]. It exhibits antioxidant properties in the membranes of cells and organelles.

Additionally, uncoupling protein activation, cell proliferation, cell signaling, and apoptosis are all significantly impacted by coenzyme Q10 via altering the permeability hole in the mitochondria (Alleva *et al*., 2001) [5]. Coenzyme Q-10 is frequently taken orally as a nutritional supplement. Coenzyme Q10 has been shown in numerous trials to be effective against UVB radiation damage, and multiple system atrophy (MSA), and as an inflammatory marker (Pastor-Maldonado *et al*., 2020) [68].

Acetyl Coenzyme A, tyrosine, phenylalanine, and seven vitamins that is vitamins B2, B3, B5, B6, B9, B12, and C are combined to form Coq10. Meat has a high concentration of coenzyme Q10 among foods) and consumption between 30 and 90 mg orally twice a day is often the advised dosage for the Q10 enzyme (Kubo *et al*., 2008) [51].

As a dietary supplement, CoenzymeQ10 comes in tablet, soft gel capsule, and oral spray form. The typical daily intake of Coenzyme Q10 is 30–90 mg, split into smaller quantities. Because Coenzyme Q 10 is fat soluble, it is highly absorbable when combined with meals high in fat. Coenzyme Q10 should be taken daily at a dose of 12 mg/kg, according to Rujiralai *et al*. (2014) [86]. Recently, Coenzyme Q10-containing nutraceuticals have become very popular in the health management space (Buettner *et al*., 2007) [17].

A clinical trial by Liu *et al*. (2016) [54] showed that following surgery, a patient with hepatocellular carcinoma who took 300 mg/day of coenzyme Q10 had a significant increase in antioxidant capacity and a decrease in levels of inflammatory

markers (hs-CRP and IL-6). Over 600 mg/kg body weight/day of Coenzyme Q10 was shown to have no observable deleterious effects in a thirteen-week canine toxicity trial. The impact of coenzyme Q10 supplementation on lipid peroxide levels and overall antioxidant status in dogs with chronic valvular heart disease was documented by Revathi *et al*. (2020) [69]. Coenzyme Q10 at a dose of 45 mg every 12 hours orally for 60 days was found to be beneficial in managing oxidative stress linked to chronic valvular heart disease in dogs when used in conjunction with therapy. The effects of supplementing with a reduced version of CoQ10 at a dose rate of 100 mg daily for 12 weeks on the antioxidant status and quality of semen were reported by Kobayashi *et al*. (2021) [50] with low-quality semen in dogs. Thus, coenzyme Q10 can be used as apotent antioxidant along with specific therapy for the treatment of various diseases in animals.

Conflict of interest

The authors have no conflict of interest.

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