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Babesiosis in Cattle

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INTRODUCTION

Cattle is an important dairy and meat producing animal playing an important role in the economy (Saunsoucy 1995; Suarez and Noh 2011; Suarez et al. 2018). *Babesia* is a protozoan parasite belonging to the genus piroplasmida, causes a deadly disease in livestock and farm animals and is transmitted by the ticks. Because the illness has direct economic effects like decreased milk output, loss of body weight, and animal death, it poses major issues for both animal life and farm economies (Menshawy 2020). It also exerts secondary costs associated with treatment and prevention (Guswanto et al. 2017). The several regions of Africa, Australia, America, and Asia, particularly India, have a great impact on the cattle industry (Bock et al. 2004; Bal et al. 2016; Hashem et al. 2018). It affects and spreads in tropical as well as subtropical countries (Beugnet and Moreau 2015; Rozej-Bielicka et al. 2015). It causes lack of appetite, fever, anemia, ceasing rumination, and increases in heart and respiratory rates. In later stages, it may lead to hemoglobinuria, a yellowish mucous membrane, and the death of animal (Wagner et al. 2002; Zintl et al. 2003; Demeke et al. 2018; Mezouaghi et al. 2019). According to (Silva et al. 2010), the Ixodidae tick can transmit the babesiosis infection to several animal species. *Babesia* (*B.*) *bovis* and *B. bigemina* are the two most important babesia species in cattle (Zintl et al. 2013). *B. divergens*, is one of the main babesia species that causes bovine babesiosis, and raised concerns among international health authorities (OIE). *Rhipicephalus* and *Ixodes* tick species can transmit babesiosis to cattle depending on the disease's type (Jabbar et al. 2015). *B. bovis and B. bigemina* can be transmitted by number of vectors including *Rhipicephalus* (*R.*) *microplus*, *R. annulatus*, and *R. geigyi*, whereas *R. decoloratus* and *R. evertsi* can only be transmited by *B. bigemina*. *Ixodes* (*I.*) *ricinus* typically transmits *B. divergens* (Bock et al. 2004; Gohil et al. 2013).

Etiology and Morphology

Babesiosis is also known by the various other names i.e., Piroplasmosis, Texas fever, and Red water fever (Sahinduran, 2012). The genus Babesia includes the two main species which are *B. bovis* and *B. bigemina* Belonging to the phylum Apicomplexa and class Sporozoasida (Allsopp et al. 1994; Radostits et al. 2006). Furthermore, the taxonomical classification of Babesia species was based on the phylogenetic analysis of 18s rRNA (Criado-Fornelio et al. 2003). Babesiosis in bovine is caused by several species of babesia i.e., *B. bovis*, *B. bigemina*, and *B. divergens* are the three most prevalent pathogenic species (Kaandorp 2004; Radostits et al. 2007; Fakhar et al. 2012). *B. bovis* infection can result in more serious illness than *B. bigemina* (Gubbels et al. 1999). The parasite *B. bovis* is located in the core of the RBCs. Its dimensions are 1.1-1.5 x 0.5-1.0 m. While *B. bigemina* is longer than other species and can be seen in pairs. It has a pear-like form. It is 1-1.5 m wide and 3-3.5 m long (Soulsby 1986; El Sawalhy 1999). According to (Jerram and Willshire 2019) and (Alvarez et al. 2019), *B. divergenis* has a small, thin, and obtuse angle (Fig. 1). Moreover, *B. major*, *B. ovata*, *B. occultaus*, and *B. jakimovi* can also infect the cattle (Menshawy 2020).

Life Cycle of Bovine Babesiosis

All species belonging to the genus *Babesia* have shown same life cycle stages with minor differences. Some species showed transovarial transmission (Babesia spp. sensu stricto) while other may be transmitted through transstadial route (*B. microti*) (Saad et al. 2015). Their life cycle can be completed in three main stages:

- Gametogony: fusion and formation of gametes occur in the gut of the ticks.
- Sporogony: It is asexual reproduction taking place in the salivary gland of tick
- Merogony: It take place in the vertebrates (Fig. 2) (Otify 2011; Abdela and Jilo 2016). Binary fission is the way of multiplication inside the red blood cells, and causing considerable pleomorphism followed by the gametocyte formation. The conjugation of gametocyte take place in the tick gut followed by the multiplication and migration to the different tissues such as salivary glands. Furthermore, the continuous development occurs in the salivary glands. The transovarial transmission may happen at this stage (Gray et al. 2010). The host will be infected when the larvae sucks the blood. The larvae transform in to the nymph after molting which is then converted in to adult. Host may get the

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Fig. 1: Babesia parasites inside red blood cells

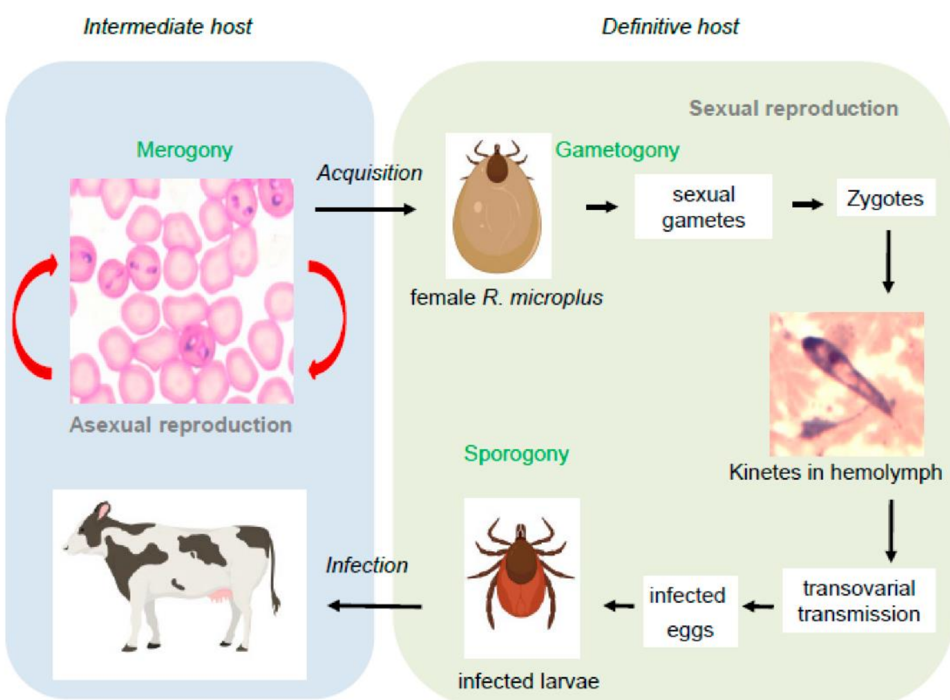

Fig. 2: Babesia Species life cycle (Gallego-Lopez et al. 2019)

infection, when vector takes a blood meal (Uilenberg 2006; Simuunza 2009; Lefevre et al. 2010; Mandal 2012; Schnittger et al. 2012; Ozubek et al. 2020).

Host Range

Out of hundred types of *Babesia* spp., only eighteen species can cause infection in domestic animals (Suarez and Noh 2011). Babesiosis mainly affects cattle, goats, sheep, horses, dogs, cats and human (Hamsho et al. 2015; Gray et al. 2019). *B. bovis* and *B. bigemina* have recently been detected in deer. The primary host for *Babesia* spp. is cattle while all other animals are considered of little epidemiological distribution (CFSPH, 2008).

Geographic Distribution

Babesiosis in cattle is present across the world due to presence of vector. However, tropical and subtropical locations frequently experience it (CFSPH, 2008). The highest prevalence of babesiosis is found in areas where ticks vector is present excessively. They are especially important in Australia, Africa, Asia, and the United States. Even while *B. bovis* typically inhabits the same habitats as *B. bigemina*, only a small number of other tick species have the ability to transmit both species. Additionally, the regional distribution of these ticks varies with the area. For instance, the two tick species can serve as a biological vector, *B. bigemina* is widely distributed in Africa (Spickler et al. 2010; Pohl 2013).

Risk Factors

Host Factors

Host factors which mainly affect the presence of disease include breed, age and immune status of the animals (Jabbar et al. 2015).

- Regarding the age of the host, the infection rate among young animals is low due to innate resistance, which is boosted by maternal antibodies passed on to calves via colostrum. This resistance gradually deteriorates, leaving the animal vulnerable to disease (Fadly 2012).
- Regarding breed, *Bos taurus* is more susceptible to babesia infection than *Bos indicus* (Radostits et al., 2007). Besides that, native breeds have higher resistance to babesiosis than foreign breeds. Because tick populations have been exposed to nature for a long time, they have developed either an innate ability or an innate resistance to progress a good immune system to the tick (Wodaje et al. 2019).
- In endemic areas, young animals can acquire passive immunity from dams via colostrum and often suffer the transient infections with mild symptoms. This infection is enough to activate active immunity and make the host a carrier for a long time. Active immunity is in charge of the carrier's persistence and premunity. These animals can be infected naturally or through chemotherapy and still have a strong immune system (Taylor et al. 2007). According to susceptibility to *B. bovis* infection, *Bos taurus* were classified into three phenotypes: 1- susceptible animals which may experience clinical signs leading to death, 2- animals having mild clinical signs, and 3- animals that are resistant and having few clinical signs (Benavides and Sacco 2007).

Pathogen Factor

Pathogenicity varies greatly depending on the strain. Because of the wide variety of strains, *B. bovis* is typically more virulent than *B. bigemina* and *B. divergens* (CFSPH 2008). Through rapid antigenic variation, various blood parasites can keep the host immune system alive (Bock et al. 2004).

Environmental Factors

The prevalence of clinical babesiosis can be varied according to seasonal variation, which also influenced by the peak of tick population. The largest prevalence occurring directly after the summit of the population of the tick. Regarding weather conditions, temperature is the most crucial factor affecting on the activity of the tick. Increase in temperature can cause the increase of the disease happenings (Menshawy et al. 2018). Cattle infection reaches the top in the summer season (El Moghazy et al. 2014; El-Bahy et al. 2018). Main economic losses happen in those places where marginal occurrence of disease is present because the population of the tick is mostly variable according to the conditions of environment (Radostits et al. 2007; Demessie and Derso 2015).

Transmission

Babesia species are biologically transmitted by vectors via transovarian transmission (first generation) and transsadial transmission (transmission of infection from egg until the adult) (Demessie and Derso 2015; Enbiyale et al. 2018). Babesiosis can be transmitted to cattle by a biological tick vector (Boophilus spp.). *Boophilus* ticks can transmit both *B. bigemina* and *B. bovis*, with nymphs and adults transmitting *B. bigemina* but only tick larvae transmitting *B. bovis* (Esmaeil et al. 2015). It is also mechanically transmitted by infected needles and syringes, blood transfusion, and surgical instruments (Menshawy 2020). *R. micropuls* (formerly *Boophilus micropuls*) and *R. annulatus* are tick vectors of *B. bigemina* (formerly *Boophilus annulatus*). Competent vectors include *R. decoloratus*, *R. geigyi*, and *R. evertsi*. *R. microplus* and *R. annulatus* are tick vectors of *B. bovis*, and *R. geigyi* can also act as its competent vector (Bock et al. 2004; De Vos and Potgieter 2004; Yadhav et al. 2015). Transplacental transmission of babesia species in cattle has also been demonstrated (De Vos and Potgieter 2004; Spickler and Anna Rovid 2016).

The Babesia species can develops and distribute throughout the organs of the ticks, infecting the salivary glands or eggs. When infected tick bites a cattle, it transferred the infection to the final host (Government and State agencies bord 2013).

Pathogenesis

There are two principal mechanisms of producing acute disease by babesia which are hemolysis and circulatory disturbance (Carlton and McGavin 1995). Sporozoites enter the host directly after tick bite and infect the erythrocytes. Within the body of the host, sporozoites will then progress into piroplasm inside the infected RBCs. This will produce 2 or 4 daughter cells and they will then leave the host cell to infect other RBCs (Hunfeld et al. 2008). They will invade other erythrocytes and can cause intravascular and extravascular hemolysis (Carlton and McGavin 1995). The rapid division of the parasite in the cells can cause rapid destruction and then haemoglobinaemia, hemoglobinuria, and fever. This can be very acute and cause death in a few days. During this process, the PCV falls to less than 20% and this will cause anemia. Clinical signs can be detected during the stage of parasitemia. At this stage, up to 45% of the red cells are infected according to Babesia species (Urquhart et al. 1996). Hemolysis also invades the release of many pharmacologically active agents (ex: proteolytic enzyme), which affect microcirculation (vasodilation, increased permeability) leading to hypotension and edema, and affect blood (viscosity, coagulation and adherence) leading to ischemia (congestion and degeneration change in tissue/organ) (Ahmed 2002). The main consequence of the disease is anemia due to hemolysis. The secondary mechanism is electrolyte imbalance. Liver and kidney degeneration are caused by lack of oxygen and perhaps by immune pathologic reaction. The kidney tubule epithelium damage will lead to impair ion exchange, which will result in hydrogen ion retention and cause acidosis (Enbiyale et al. 2018).

Clinical Signs

Incubation period ranges between eight and fifteen days in natural infection. Before the onset of other clinical signs fever (>40°C) usually appears (OIE 2010). The clinical signs are different according to the age and species of the animals, parasite strain, immunological status, concurrent infection with other pathogens, and genetic factors in the dose of the inoculated parasites. Most cases have been detected in animals less than 9 months of age usually staying asymptomatic (Anon 2008).

Babesiosis clinical signs include emaciation, ataxia, loss of appetite, stop rumination, loss of body weight, progressive hemolytic anemia, jaundice (Icterus), yellowish color of conjunctival as well as vaginal mucous membranes in more advanced cases; hemoglobinuria, problems in the heart and respiratory rates, and a decrease in milk yield. In some cases, fever during an infection causes abortion in cattle. Patients experience general circulatory shock and, in some cases, nervous symptoms due to the sequestration of the infected RBCs in cerebral capillaries (Zintl et al. 2003; Khan et al. 2004; Akande et al. 2010; Chaudhry et al. 2010; Rashid et al. 2010; Terkawi et al. 2011; Onoja et al. 2013; El Moghazy et al. 2014; Bhat et al. 2015; Masih et al. 2021).

Dark red urine is one of the clinical signs of babesia (Yadav et al. 2004). The main clinical signs of *B. bigemina* are fever, hemoglobinuria, and anemia (Zintl et al. 2013).

Diagnosis

Detection of active cases of babesiosis is based mainly on several diagnostic techniques as
follow:

Microscopic Examination

The conventional model of babesiosis examination is a direct examination under a microscope. It is used to identify the agent in the infected host. This is accomplished by examining thick and thin films and then staining them with Giemsa or Romanowsky stain. Thick films can detect parasites as few as one parasite out of 106 RBCs (Kahn 2005). Microscopic examination is still the most cost-effective and time-efficient technique for identifying Babesia parasites (Hamoda et al. 2014). Giemsa-stained thin blood smears are the traditional and gold standard for identification (Nayel et al. 2012) and serve as an ideal method for species differentiation. It is adequate for detecting acute infections but has lower effects in cases of low parasitemia in carriers (Criado-Fornelio et al. 2009; Bal et al. 2016; Shang et al. 2016; Masih et al. 2021).

Serological Examinations

To detect antibodies in subclinical cases and avoid the drawbacks of microscopic examination, the Indirect Fluorescent Antibody Test (IFAT) and Enzyme-Linked Immunosorbent Assay (ELISA) are used (El-Fayomy et al. 2013). These tests have low sensitivity and frequently fail to distinguish between chronic and acute infections (Mahmoud et al. 2016). These tests produce false-positive and false-negative results due to cross-reactive antibodies (Esmaeil et al. 2015). Another point to consider is that antibodies persist even months after infection, implying that no active infection exists. As a result, these will be unable to reveal the precise prevalence at a given time (Abdel Aziz et al. 2014). The most common test for detecting antibodies in babesia species is IFAT (Chaudhry et al. 2010). Anonymous (2008) described a complement fixation (CF) test for detecting antibodies to *B. bovis* and *B.bigemina*.

Molecular Diagnosis

Molecular diagnosis is used to identify nucleic acids which is considered as an indirect identification. However, both sensitivity and specificity are very high (Mosqueda et al. 2012). The most sensitive and specific technique for the detection of babesiosis is (PCR) Polymerase chain reaction (Vannier and Krause 2009; AbouLaila et al. 2010) and useful for the detection of infection in the early stage. It has been reported that the PCR technique is much more sensitive than microscopy for the identification of babesiosis. It is an important test for confirmation in some cases for regulatory testing (Shams et al. 2013; Sharma et al. 2016; Bal et al. 2016).

Differential Diagnosis

Like many other infectious diseases, babesiosis also causes fever and anemia. Anaplasmosis, theileriosis, trypanosomiasis, leptospirosis, rapeseed poisoning, and chronic copper poisoning can be counted as a differential diagnosis of babesiosis. Rabies and other encephalitis's can also be considered in cattle with CNS signs (Spickler and Anna Rovid 2016).

Treatment

The successful treatment of babesiosis is dependent on the use of effective drugs and early detection (Vial and Gorenflot 2006). Trypan blue, which was first used against *B. bigemina* but has no effect on *B. bovis*, was one of the most effective drugs used to treat bovine babesiosis. It is rarely used because it discolors the flesh of animals. In the tropics, diminazene aceturate is currently used as a babesiacide. It has been withdrawn from the market in Europe for marketing reasons (Sayin et al. 1997). Imidocarb, which is primarily used in animals, is another effective drug for treating babesiosis. This drug can also be used to prevent babesiosis and anaplasmosis. Imidocarb can linger in tissues for a long time (Hashem et al. 2018) However, acridine and quinuronium derivatives can be used as effective drugs as well. Many European countries used the babesiacides quinuronium sulfate, amicarbalide, diminazene aceturate, and imidocarb diproprionate against bovine babesiosis for several years, but quinuronium sulfate and amicarbilide were withdrawn due to manufacturing safety issues (Vial and Gorenflot 2006). The combination of imidocarb dipropionate and oxytetracycline is the most effective treatment for Babesiosis in small ruminants (Ijaz et al. 2013). Beside this, in severe cases, supportive therapy is also required (Zintl et al. 2013). Vitamin E can also be used as a supportive therapy because it reduces the oxidative effect of babesia by increasing antioxidant activity (Abdel Hamid et al. 2014).

Prevention and Control

In the world, several countries have not completely controlled bovine babesiosis, despite the availability of live attenuated vaccine (De Vos and Bock 2000; Florin-Christensen et al. 2014). This can confirm the quick action for crucial vaccines to prevent the development of acute disease as well as parasite distribution into non-endemic areas. Bovine babesiosis control is currently under threat because of climate changes that act on vector development and expansion (Dantas-Torres 2015; Sonenshine 2018).

Control of this disease is created by accurate diagnosis, perfect treatment, and prevention of babesiosis (Mylonakis 2001). Animals after recovering from infection remain immunized. The parasite can persist in the peripheral blood for several years in *B. bovis* cases and for many months in *B. bigemina*, and no signs are apparent during this carrier state, so the animal should be monitored and treated after infection to prevent the distribution of disease to other animals (El Sawalhy 1999). Prevention and control of babesiosis can actively be maintained by the following methods: immunization, chemoprophylaxis, and vector control (Suarez and Noh 2011; ILRAD 1991). The combination of these three methods is also a choice. Tick control by vaccination has been stated as a useful way in Australia (Lightowlers 2013). A research has reported that using combined chemotherapeutics is more effective for parasite elimination and results in decreasing the risk of drug resistance (Pritchard et al. 2013). The advantages of mixing of the chemotherapeutics include highly effectiveness, reduction in the dose (which may lead to reduced side effects) and lowering of drug resistance. According to the US reports, Babesiosis can be controlled and eradicated by eliminating the host tick(s). This will be done by using acaricides every two to three weeks. In those countries where eradication is not applicable, tick control can reduce the incidence of disease (APHIS 2010). Chemotherapy is another important method for controlling bovine babesiosis, either in the field or to control artificially induced infections. Chemotherapy is critical in some parts of the world to eradicate and prevent babesiosis. Infected animals should be treated with antiparasitic drugs as soon as possible in countries where the disease is endemic. The success of disease treatment is dependent on early diagnosis and proper administration of the drug of choice (Fernandez and White 2010; Georgiou et al. 2015). Use of living attenuated vaccine is the cornerstone to control and prevent babesiosis in many countries like Argentina, Israel, and Australia. However, this live vaccine is not cheap to produce and has many limitations (Brown et al. 2006; Florin-Christensen et al. 2014; Costamagna et al. 2016; Aranda et al. 2017; Suarez et al. 2018). Vaccines are provided in frozen form. Live babesia vaccines are not completely safe. A single dose can immunize animals against babesiosis over life (Saad et al. 2015).

Immunization of the animals in a prophylactic way has been stated as the most efficient way to decrease losses happened by bovine babesiosis. Live attenuated vaccine from the *B. bovis* or *B. bigemina* strain is used to immunize cattle in many countries. These vaccines are important due to having safety issues such as the potential effect for virulence in adult animals, contamination possibly occurring with other etiological agents, and blood protein hypersensitivity reactions (OIE 2015).

Conclusion

Babesiosis is a severe disease not only in cattle and other domestic and wild animals but also in human beings. It has significant impacts on both the economic and medical processes. It can cause impairment in the trade of animal products such as milk, meat, and hide by decreasing their quality. It has been reported that imidocarb and diminazene aceturate used as a treatment of babesiosis for many years, but nowadays, several compounds are progressed and assessed as a treatment. This can offer a good point for disease control. Controlling tick-borne diseases is important in developing livestock health services products. Control strategies can be different from country to country and place to place and the most important ones are vaccines and drugs.

Recommendations

- Knowledge, as well as awareness, should be given to the owners about the transmission way, prevention, and control of babesia.
- Governments and organizations should give attention to control and eradicate babesiosis in order to improve the economy.
- The surveillance system is important in Kurdistan Region to prevent bovine babesiosis.

New drugs and vaccines should be developed to eradicate the carrier states.

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