International Journal of Research in Pharmacy and Life Sciences

Journal Home Page: www.pharmaresearchlibrary.com/ijrpls

Review Article **Open Access**

An Overview of Babesiosis

P. Sri Chandana yadhav*, M.V. Sai lalith kumar, Y.N. Sujitha, M. Lavanya, Ch. Madhavilatha

Department of Pharmacology, Narayana Pharmacy College, Chinthareddypalem, Nellore.

A B S T R A C T

Babesiosis is an infection caused by a malaria-like parasite, also called a piroplasm, [genus-Babesia, phylum- Apicomplexa] that infects red blood cells. The first case of babesiosis was reported from Nantucket Island, Massachusetts, in 1969. Over 100 distinct species have since been identified within the *Babesia* genus, though only a few of these are currently known to be human pathogens. The disease manifestations of human babesiosis are caused by the asexual reproductive stage of the organism in the erythrocytes of the host and the subsequent lysis of host cells. Most cases of B. microti infection are mild and usually resolve on their own, without treatment. Significant effort has been invested in the development of vaccines for cattle andother animals, however, which might eventually prove useful for developing a human vaccine. Much of the work done to develop vaccines has focused on the large babesias, such as B. bovis, B. divergens, and B. bigemina . In more severe cases, however, a combination of clindamycin and quinine is administered as the standard treatment. At the present time, there are no vaccines for humans against babesial organisms, nor is infection frequent enough at present to warrant a large-scale vaccine effort. Further studies using the molecular tools now available and those to be developed will lead to a better understanding of the natural history of these organisms, including the transmission cycle and the potential role of Babesia parasites themselves as immunomodulators.

Keywords: *Clindamycin, quinine, B. bovis, B. divergens and B. bigemina*

A R T I C L E I N F O

CONTENTS

Article History: Received 20 October 2014, **Accepted** 21 December 2014

***Corresponding Author**
P. Sri Chandana yadhav
Narayana Pharmacy College,
Chinthareddypalem, Nellore.
Manuscript ID: IJRPLS2360

PAPER-QR CODE

Citation: P. Sri Chandana yadhav, et al. An Overview of Babesiosis. *Int. J. Res. Pharm, L. Sci*., 2015, 3(1): 287-295.

1. Introduction

Babesiosis is an infection caused by a malaria-like parasite, also called a piroplasm, [genus-Babesia ,phylum-Apicomplexa] that infects red blood cells. The first case of babesiosis was reported from Nantucket Island, Massachusetts, in 1969. Over 100 distinct species have since been identified within the Babesia genus, though only a few of these are currently known to be human pathogens. This parasite infects the red blood cells. It is a treatable disease spread in nature by the bite of certain types of ticks. These ticks carry microscopic parasites that can infect and destroy red blood cells in humans. People can get infected with Babesia parasites in several ways by the bite of an infected tick (most common), by getting a blood transfusion from an infected donor of blood products, by congenital transmission from an infected mother to her baby (during pregnancy or delivery). The diagnosis of babesiosis is based on epidemiologic, clinical, and laboratory information. patients experience a viral infection like illness with fever, chills, sweats, myalgia, arthralgia, anorexia, nausea, vomiting, or fatigue. On physical examination, fever, splenomegaly, hepatomegaly, or jaundice may be observed.

Figure 1: Tick Which Cause Babesiosis

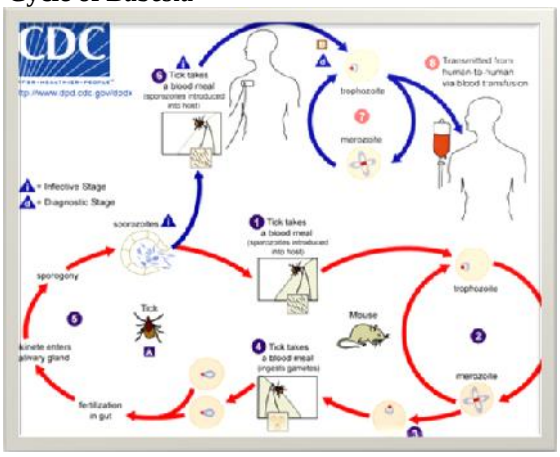
2. Classification

Babesia are classified as apicomplexan parasites of the suborder Piroplasmidea and family Babesiidae on the basis of their exclusive invasion of erythrocytes, multiplication by budding rather than schizogony, and lack of hemozoin.

Parasite species	Vertebrate hosts	Disease	Pathogeni city	Vectors	Distribution
B. bovis (argentina)	cattle, deer	redwater fever	High	Ixodes, Rhipicephalus (Boophilus)	Europe, Africa, Australia, South & Central America
B. bigemina	cattle, deer	redwater fever	moderate	Haemaphysalis, Rhipicephalus (Boophilus)	Europe, Africa, Australia, South & Central America
B. divergens	Cattle	redwater fever	moderate	Ixodes	Western & Central Europe
B. major	Cattle		Low	Rhipicephalus (Boophilus)	Europe, Russia
B. equi	horses, zebra	biliary fever	High	Dermacentor, Hyalomma, Rhipicephalus (Boophilus)	Southern Europe, Africa, Asia, South America
B. caballi	Horses		moderate	Dermacentor, Hyalomma, Rhipicephalus (Boophilus)	Dermacentor, Hyalomma, Rhipicephalus (Boophilus) Southern Europe, Russia, Africa, Asia
B. ovis	sheep, goats		Low	Rhipicephalus (Boophilus), Ixodes	Southern Europe, Africa, Asia, tropical America

B. motasi	sheep, goats		moderate	Rhipicephalus (Boophilus), Haemaphysalis, Dermacentor	Southern Europe, Africa, Asia, tropical America
B. trautmanni	Pig		moderate	Rhipicephalus	Southern Europe, Africa
B. canis	Canids	tick fever	high	Rhipicephalus, Dermacentor, Haemaphysalis	Southern Europe, Africa, Asia, South & North America
B. gibsoni	Canids	tick fever	High	Rhipicephalus, Haemaphysalis	India, Ceylon, China
B. felis	cats, lion, leopard		moderate	Haemaphysalis	Africa, India
B. microti	Rodents		Low	Ixodes	Worldwide
B. rodhaini	Rodents		Low	unknown	Africa

Life Cycle of *Babesia*



In Mouse:

- The cycle begins when an infected tick sends sporozoites into a mouse while taking a blood meal .
- The sporozoites then go into red blood cells, where they asexually reproduce by budding .
- The babesia then differentiate into male and female gametes . The gametes are once again ingested by the tick , where the they join and undergo the sporogonic, producing sporozoites .
- Vertical transmission occurs in some types of Babesia, but not *B. microti*.

In Human:

- Allspecies of babesia are naturally transmitted by the bite of infected ticks (almost all ixodids rather than argasids)and the main lifecycle difference amounts to the presence of transovarial transmission in some species (Babesia spp.sensu stricto) and not in others (B. microti-like).
- During the tick bite, sporozoites are injected into the host anddirectly infect red blood cells .
- This phenomenon separates Babesia spp. from Theileria spp., where sporozoites do not readily infect red blood cells but initially penetratea lymphocyte or macrophage in which developmentinto schizonts takes place .
- In the host, babesia sporozoites develop into piroplasms inside the infected erythrocyte resulting in two or sometimes four daughter cells that leave the host cell to infect other erythrocytes until the host dies or the immunity of the host clears the parasites.
- The spleen with its lympho-reticular filter function is essential in resisting primary infections of Babesia spp. by specifically removing infected cells from circulation, probably through a combination of spleen microcirculation and stimulated phagocytic cell activity.

3. Pathogensis

The primary pathological event in heavy infection is haemolysis, resulting in haemolytic anaemia and jaundice. In the absence of aggressive intervention, the anoxia and toxiceffects that follow often lead to organ failure and death. Parasitaemias do not always relate directly to the degree of anaemia, suggesting that erythrocyte destruction is due not only to lysis of infected cells and liver macrophages. Some symptoms, such as fever, myalgia, renalin sufficiency ,coagulo pathy, and hypotension, that occur in B. microti infections with parasitaemias of less than1%,maybecause by excessive production of pro-inflammatory cytokines, as in malaria.

4. Epidemiology

All Babesia are transmitted by ticks with a limited host range. The principal vectors of B. bovis and B. bigemina are Rhipicephalus spp. ticks and these are widespread in tropical and subtropical countries. The major arthropod vector of B. divergens is Ixodes ricinus. BB is principally maintained by subclinically infected cattle that have

recovered from disease. Morbidity and mortality vary greatly and are influenced by prevailing treatments employed in an area, previous exposure to a species/strain of parasite, and vaccination status. In endemic areas, cattle become infected at a young age and develop a long-term immunity. However, outbreaks can occur in these endemic areas if exposure to ticks by young animals is interrupted or immuno-naïve cattle are introduced. The introduction of Babesia infected ticks into previously tick-free areas may also lead to outbreaks of disease.

Hosts

B. bovis and B. bigemina

a. cattle
b. water buffalo (Bubalus bubalis) and African buffalo (Syncerus caffer)
c. reports of disease in white-tailed deer (Odocoileus virginianus) in Mexico

B. divergens

a. Cattle And Reindeer (Rangifer tarandus)
b. Mongolian gerbils (Meriones unguiculatus); other peridomestic rodents are resistant to disease.
c. Splenectomised humans and non-human primates are highly susceptible.
d. Experimental infection with no clinical signs have been documented in splenectomised ungulates including mouflon (Ovis musimon), red deer (Cervus elaphus), roe deer (Capreolus capreolus), and fallow deer (Dama dama).

Transmission:

a. BB is principally transmitted by means of ticks
b. Tick vectors of Babesia bigemina: Rhipicephalus microplus (formerly Boophilus microplus) and Rhipicephalus annulatus (formerly Boophilus annulatus); Rhipicephalus decoloratus, Rhipicephalus geigyi, and Rhipicephalus evertsi are also competent vectors
c. B. bigemina transmitted by feeding of adult and nymphal stages of one-host Rhipicephalus spp. ticks Tick vectors of Babesia bovis: Rhipicephalus microplus and Rhipicephalus annulatus; Rhipicephalus geigyi is also a competent vector
d. B. bovis transmitted by feeding of larval stages of one-host Rhipicephalus spp. ticks .

Babesia may also be transmitted by fomites and mechanical vectors contaminated by infected blood . Infections are transmitted by ixodid (hard-bodied) ticks which may be one-, two- or three-host ticks. Ingested parasites develop into large motile vermicules which migrate through the body of the tick and then undergo sporogony. Parasites undergo trans-stadial transmission, whereby infections persist during metamorphosis from larvae to nymphs to adults. They also undergo transovarian transmission, where parasites infect developing eggs in engorged female ticks, so nearly all the progeny are born already infected. Eventually, hundreds of small pyriform bodies (sporozoites) are formed within salivary cells and are injected into mammalian hosts during feeding.

Signs and Symptoms:

The disease manifestations of human babesiosis are caused by the asexual reproductive stage of the organism in the erythrocytes of the host and the subsequent lysis of host cells. Consequently, there is a very broad clinical spectrum which is probably directly reflective of the level of parasitemia in the blood. The incubation period from the time of tick transmission of the organism to the appearance of symptoms varies from 1 to 6 weeks and may be as long as 3 months . Host factors associated with the biological variation in disease presentation are poorly understood.The extreme end of the spectrum is often described as a fulminating malaria-like infection; symptoms may include malaise,chills, myalgia, anemia, fatigue, and fever (which can be ashigh as 40°C). Some cases also described nausea, emesis, night sweats, weight loss, and hematuria, which are believed to be associated with higher levels of parasitemia .Hepatomegaly

and splenomegaly may also be present. Hemolyticanemia that lasts for several days to a few months can occur in clinically severe cases, most commonly in asplenic or elderly hosts. Complications are more likely in immune compromised patients and can include worsening of an already weakened state or, rarely, adult respiratory distress syndrome. The cases due to B. divergens infections seen in Europe are

usually more severe than those caused by B. microti. Onset of disease symptoms usually occurs within 1 to 3 weeks of the infecting tick bite (69). Most patients had been splenectomized prior to infection. Illness appears suddenly, with hemoglobinuria as the presenting symptom followed by jaundice due to severe hemolysis. In the most severe cases, patients develop a shock-like picture, with renal failure and pulmonary edema. The presence or absence of many laboratory manifestations generally depends on the level of parasitemia . Clinically apparent cases may develop high levels of transaminases, alkaline phosphatases, unconjugated bilirubin, and lactic dehydrogenase in serum. Normochromia, normocytic anemia, thrombocytopenia, and, occasionally, leukopenia may also be present. This may be due to TNF-mediated inflammation responses, similar to the pathogenesis of severe malarial infections.However, in light of the recent recognition of coinfection in humans with multiple tick-transmitted agents, it is possible that some of the more variable aspects of the disease could also be associated with coinfection.

5. Diagnosis

Incubation period is often 2–3 weeks or longer after tick infestation. Shorter incubation periods have however been documented in the field and through experimental inoculation (4–5 days for B. bigemina and 10–12 days for B. bovis).

Clinical diagnosis

Clinical manifestations of disease associated with BB are typical of a haemolytic anaemia disease process but vary according to agent (i.e. species of parasite) and host factors (i.e. age, immune status). BB is predominantly observed in

adult cattle with B. bovis generally being more pathogenic than B. bigemina or B. divergens. Infected animals develop a life-long immunity against re-infection with the same species and some cross-protection is evident in B. bigemina-immune animals against subsequent B. bovis infections.

Babesia bovis

- High fever
- Ataxia and incoordination
- Anorexia
- Production of dark red or brown-colored urine
- Signs of general circulatory shock
- Sometimes nervous signs associated with sequestration of infected erythrocytes in cerebral capillaries
- Anaemia and haemoglobinuria may appear later in the course of the disease
- In acute cases: maximum parasitaemia (percentage of infected erythrocytes) in circulating blood is often less than 1%

Babesia bigemina

- Fever
- Haemoglobinuria and anaemia
- Production of dark red or brown-colored urine
- Nervous signs minimal or non-existent as intravascular sequestration of infected erythrocytes does not occur
- Parasitaemia often exceeds 10% and may be as high as 30%

Babesia divergens

- Parasitaemia and clinical appearance are similar to B. bigemina infections

Lesions

- Lesions observed are those most often associated with an intravascular haemolytic condition
- Pale or icteric mucous membranes; blood may appear thin and watery
- Subcutaneous tissues, abdominal fat and omentum may appear icteric
- Swollen liver with an orange-brown or paler coloration; enlarged gall bladder containing thick, granular bile
- Enlarged, dark, friable spleen
- Kidneys appear darker than normal with possible petechial haemorrhages
- Bladder may contain dark red or brown-colored urine
- Possible oedema of lungs
- Petechiae or ecchymoses on surface of heart and brain

Differential diagnosis

- Anaplasmosis
- Trypanosomiasis
- Theileriosis
- Bacillary haemoglobinuria
- Leptospirosis
- Eperythrozoonosis
- Rapeseed poisoning
- Chronic copper poisoning

Laboratory diagnosis

Samples

a. Several thick and thin blood smears collected from superficial skin capillaries (e.g. tip of the ear or tip of the tail) of live animals during the acute phase of the disease (appearance of fever)
b. Thin blood films should be air-dried, fixed in absolute methanol for 1 minute and stained with 10% Giemsa stain for 20–30 minutes
c. Blood films should be stained as soon as possible after preparation to ensure proper stain definition
d. Thick films are made by placing a small drop (approximately 50 µl) of blood on to a clean glass slide and spreading this over a small are using a circular motion eith the corner of another slide. The droplet is air-dried, heat-fixed at 80°C for 5 minutes, and stained (without fixing in methanol) in 10% Giemsa for 15 minutes.
e. Unstained blood films should not be stored with or near formalin solutions as formalin fumes may affect staining quality; moisture also affects staining quality.
f. If it is not possible to make fresh films from capillary blood, sterile jugular blood should be collected into an anticoagulant such as lithium heparin or ethylene diamine tetra-acetic acid (EDTA).
g. The sample should be kept cool, preferably at 5°C, until delivery to the laboratory B. bovis is sequestered and found in higher numbers in capillary blood, B. bigemina and B. divergens parasites are uniformly distributed through the vasculature.
h. Samples from dead animals should consist of thin blood films, as well as smears from organs.
i. Organ smears acquired at necropsy: cerebral cortex, kidney (freshly dead), spleen (when decomposition is evident), heart muscle, lung and liver.
j. Organ smears are made by pressing a clean slide on to a freshly cut surface of the organ or by crushing a small sample of the tissue (particularly cerebral cortex).
k. Between two clean microscope slides drawn lengthwise to leave a film of tissue on each slide.
l. Organ smear is then air-dried (assisted by gentle warming in humid climates), fixed for 5 minutes in absolute methanol, and stained for 20–30 minutes in 10% Giemsa.
m. Especially suitable for the diagnosis of B. bovis infections using smears of cerebral cortex but unreliable if sample taken 24 hours or longer after death has occurred, especially in warmer weather.
n. Babesia parasites can sometimes be detected in capillary blood taken from the lower limb region one or more days after death.
o. Serum samples should also be collected.

Procedures

a. Identification of the agent
b. Microscopic examination of blood – traditional method of identifying agent in infected animals by microscopic examination of Giemsa-stained thick and thin blood films
c. Stained films are examined under oil immersion using (as a minimum) a ×8 eyepiece and a ×60 objective lens.
d. Morphology of Babesia described in various sources, including OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals.
e. sensitivity of thick films can detect parasitaemias as low as 1 parasite in 106 red blood cells.
f. Babesia species differentiation is good in thin films but poor in the more sensitive thick films.
g. Adequate for detection of acute infections, but not for detection of carriers where parasitaemias are very low.
h. Parasite Identification and differentiation improved by using a fluorescent dye, such as acridine orange instead of Giemsa.
i. Nucleic acid-based diagnostic assays - very sensitive particularly in detecting B. bovis and B. bigemina in carrier cattle.
j. A PCR- based techniques are reported to be at least 1000 times more sensitive than thin blood smears for detection of B. bovis.
k. A number of PCR techniques have been described that can detect and differentiate species of Babesia in carrier infections.
l. Current PCR assays generally do not lend themselves well to large-scale testing; unlikely to supplant serological tests as the method of choice for epidemiological studies.
m. PCR assays are useful as confirmatory tests and in some cases for regulatory testing.

***In-vitro* culture methods**

a. Used to demonstrate presence of carrier infections of Babesia spp. B. bovis has also been cloned in culture.
b. Minimum parasitaemia detectable by this method depends on the facilities available and the skills of the operator but could be as low as 10–10, making it a very sensitive method for the demonstration of infection, with 100% specificity.
c. Animal inoculation is not suitable for diagnostic purposes.

Serological tests

- Babesia bovis enzyme-linked immunosorbent assay
- ELISA for diagnosis of B. bovis infection uses a whole merozoite antigen; undergone extensive evaluation
- Competitive ELISAs using recombinant merozoite surface and rhoptry associated antigens of B. bovis have recently been developed
- Reduction in specificity of the indirect B. bovis ELISA using recombinant antigens has been noted in some situations
- Babesia bigemina enzyme-linked immunosorbent assay
- a competitive ELISA developed and validated in Australia and USA are apparently the only ELISAs in routine use. It has been included in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
- no other well-validated ELISA available for B. bigemina; due in part to the fact that antibodies to B. bigemina crude antigen typically have poor specificity
- ELISAs have also been developed for B. divergens using antigen derived from culture, Meriones or cattle, but none has been validated internationally
- An immunochromato-graphic test for simultaneous rapid serodiagnosis of bovine babesiosis caused by B. bovis and B. bigemina was developed recently .
- Indirect fluorescent antibody (IFA) test .
- widely used in the past to detect antibodies to Babesia spp., but the B. bigemina test has poor specificity.
- cross-reactions with antibodies to B. bovis in the B. bigemina IFA test are a particular problem in areas where the two parasites coexist .
- disadvantages of low sample throughput and subjectivity .

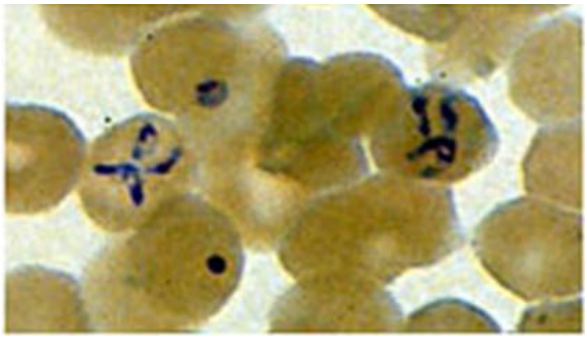


Figure 2

6. Treatment

Most cases of B. microti infection are mild and usually resolve on their own, without treatment. In more severe cases, however, a combination of clindamycin and quinine is administered as the standard treatment. This particular therapeutic regimen was discovered during the management of a case of presumed transfusion-acquired malarial infection . Initially, chloroquine was used to treat the patient, which proved to be unsuccessful in resolving the infection. The patient was then treated with quinine and clindamycin, which successfully eradicated the organisms. Subsequent studies in animals have supported the usefulness of this combination of antimicrobial agents . Comparisons between the duration of B. microti DNA (parasitemia) in babesiosis patients who were treated with quinine and clindamycin and babesiosis patients who were untreated showed that treatment reduces the duration of parasitemia. However, the potential for drug-related toxicity with this regimen is significant and includes hearing loss,

tinnitus, syncope, hypotension, and gastrointestinal distress. In very serious cases, anti-infective therapy might not be sufficient, and procedures such as erythrocyte exchange transfusion can be beneficial or even life-saving. Patients who are iatrogenically immunosuppressed, HIV infected , or severely infected with Babesia sometimes do not respond to antimicrobial therapy and require extra treatment. Alternative combinations for treatment are being investigated because of the occasional failure and frequent toxicity of quinine and clindamycin. Studies with hamster models have shown that antimalarial agents are ineffective for B. microtiinfections in vivo .Patients with B. divergens infections, regarded as medical emergencies, require prompt treatment that includes erythrocyte exchange transfusion along with intravenous clindamycin and oral quinine to arrest hemolysis and prevent renal failure. In vitro evaluations of B. divergens and its suscepti-bility to various antimicrobial agents also demonstrated that Imidocarb and the combination of oxomemazine and phenamidine were most effective in vitro . Imidocarb has not been approved for use in humans. There have been reports of success with other agents, such aspentamidine and cotrimoxazole,but the side effects of pentamidine make this course of treatment less desirable .Furthermore, one study in dogs showed that pentamidine was effective in arresting or reversingthe progression of the disease but not in clearing the organisms from the blood.

Vaccines:

At the present time, there are no vaccines for humans against babesial organisms, nor is infection frequent enough at present to warrant a large-scale vaccine effort. Significant effort has been invested in the development of vaccines for cattle andother animals, however, which might eventually prove useful for developing a human vaccine. Much of the work done to develop vaccines has focused on the large babesias, such as B. bovis, B. divergens, and B. bigemina . Vaccine development has resulted in attenuated vaccines, vaccines that use soluble antigens from *in-vitro* cultures and recombinant vaccines. Comparisons of various aspects of attenuated and virulent strains have furthered our understanding of the disease process and helped us to identify potential key components that are involved, such as the genes specific to virulent and attenuated or avirulent strains. Studies aimed at the development of vaccines against various species of Babesia have also helped elucidate some of the immune mechanisms that occur in response to the infection process. Should vaccines eventually provide effective protection, they might become useful for splenectomized or immunocompromised patients living in high-risk areas.

Live vaccines:

The use of living parasites to immunize cattle against the spread of babesiosis has been employed for a long time in livestock management with varying success. In 1964, an attenuated strain of B. bovis was produced by adaptation in splenectomized calves. This strain has proved to be a very useful vaccine. Since then, numerous attenuated vaccines have been developed for several Babesia species.

Recombinant vaccines: Although attenuated vaccines have been effective, they have several problems associated with them; among the most important is the cotransmission of other enzootic agents, such as bovine leukosis virus, and a short shelf life . Therefore, there are studies targeted at developing other preventive techniques. Irradiated B. bovis-, B. bigemina-, and Babesia major-infected erythrocytes have been used to prevent parasitemia but are not as effective as other vaccines. Research for recombinant vaccines has focused on developing vaccines from the major surface antigens of the sporozoite form. In particular, the apical complex proteins are of special interest because of their putative role in host cell invasion.Antigens from these proteins have been shown to elicit an immune response that could be sufficient for protection. Several candidate proteins have been identified in Babesia species, including the rhoptry-associated proteins (RAP), which are encoded by a multigene family. RAP-1 from both B. bovis and B. bigemina is highly immunogenic for both B and T cells, elicits a Th1-type response from T helper cells, and can induce partial protective immunity against challenge. However, the presence of specific RAP-1 antibodies does not consistently correlate with the degree of protective immunity , implying a more elaborate role for both the effector and helper functions of CD41 T cells. Additionally, the immune effector mechanisms responsible for protection require more elucidation to select an appropriate antigen delivery system. It is clear that many facets of the babesial life cycle and infectious process still need to be clarified to aid in vaccine development.

Prevention and Control:

Sanitary prophylaxis

a. Eradication of BB has been accomplished by elimination of tick vector and/or intensive chemotherapeutic regimes.
b. In areas where eradication of tick is not feasible or desirable, ticks are controlled by repellents and acaricides.
c. Reducing exposure of cattle to ticks.
d. repellents, acaricides and regular inspection; animals and premises.
e. Control and eradication of the tick vector.
f. Cattle develop a durable, long-lasting immunity after a single infection with B. bovis, B. divergens or B. bigemina, a feature that has been exploited in some countries to immunise cattle against babesiosis.
g. Endemic environments should be monitored carefully introduction of immuno-naïve animals .
h. Introduction of new species or strains of disease agent.
i. Interruptions in exposure to ticks and disease due to changes in climate, host factors and management.
j. Special care in possible mechanical infection of horses with contaminated blood.
k. Medical prophylaxis

Vaccine for Babesia:

a. Live vaccine: most live vaccines contain specially selected strains of Babesia (mainly B. bovis and B. bigemina) and are produced in calves or in vitro in

government-supported production facilities as a service to the livestock industries .

c. lead to hypersensitivity reactions; usually used in younger animals.
d. An experimental B. divergens vaccine prepared from the blood of infected Meriones has also been used successfully.

Other vaccines

a. Despite the worldwide efforts, the prospects for recombinant vaccines against Babesia spp. Remain challenging.
b. To date, no effective subunit vaccine is available commercially.
c. Experimental vaccines containing antigens produced in vitro have been developed but the level and duration of protection against heterologous challenge are unclear**.**
d. Endemic areas**.**

b. Caution should be used in their employment as they may be virulent in adult animals, may be contaminated with other disease agents and could
e. Killed vaccine: prepared from blood of B. divergens-infected calves; little information available on level and duration of the conferred immunity.

e. Clinically affected animals treated with an antiparasitic drug (diminazene diaceturate, imidocarb, amicarbalide); efficacy depends on timely detection early in disease.
f. Babesia parasites can be cleared from carrier animals; reduces clinical signs.
g. Imidocarb has been reported to protect animals from disease but allow development of immunity; caution in regard to residues in milk and meat.
h. Consideration can be given to blood transfusions and other supportive therapy, if appropriate.

7. Conclusion

Human babesiosis was first described in 1957 but is now known to have worldwide distribution. The increase in reported cases is likely due to increases in actual incidence as well as increased awareness of the disease. Despite the diagnostic and preventive advances resulting from extensive research and a greater understanding of the disease, babesiosis continues to have significant medical impact as a confounding variable in the diagnosis and treatment of Lyme disease and as a potential threat to the blood supply, especially in the United States. Diagnostic advances, like the development of PCR assays, have resulted in increased sensitivity for detection as well as the discovery and characterization of new babesial species. Further studies using the molecular tools now available and those to be developed will lead to a better understanding of the natural history of these organisms, including the transmission cycle and the potential role of Babesia parasites themselves as immunomodulators.

8. References

1. Allsopp MT, Allsopp BA. Molecular sequence evidence for the reclassification of some Babesia species. Ann N Y Acad Sci. **2006**, 1081: 509-17.
2. Cantu A, Ortega-S JA, Mosqueda J, Garcia-Vazquez Z, Henke SE, George JE. Immunologic and molecular identification of Babesia bovis and Babesia bigemina in free-ranging white-tailed deer in northern Mexico. J Wildl Dis., **2007**, 43: 504-7.
3. Hilpertshauser, H., Deplazes, P., Schnyder, M., Gern, L., Mathis, A., **2006**. Babesia spp. identified by PCR in ticks collected from domestic and wild ruminants in southern Switzerland. Appl. Environ. Microbiol. 72, 6503–6507.
4. Hunfeld KP, Hildebrandt A, Gray JS. Babesiosis: recent insights into an ancient disease. Int J Parasitol. **2008**, 38: 1219-37.
5. Krause, P.J., Spielman, A., Telford III, S.R., Sikand, V.K., McKay, K., Christianson, D., Pollack, R.J., Brassard, P., Magera, J., Ryan, R., Persing, D.H., **1998**. Persistent parasitemia after acute babesiosis. N. Eng. J. Med. 339, 160–165.
6. Conrad, P.A., Kjemtrup, A.M., Carreno, R.A., Thomford, J., Wainwright, K., Eberhard, M., Quick, R., Telford 3rd, S.R., Herwaldt, B.L., **2006**. Description of Babesia duncani n.sp. (Apicomplexa: Babesiidae) from humans and its differentiation from other piroplasms. Int. J. Parasitol. 36, 779–789.
7. Denes, E., Rogez, J.P., Darde, M.L., Weinbreck, P., 1999. Management of Babesia divergens babesiosis without a complete course of quinine treatment. Eur. J. Clin. Microbiol. Infect. Dis. 18, 672–673.
8. de Vos, A.J., Dalgliesh, R.J., Callow, L.L., **1987**. Babesia. In: Soulsby, E.J.L. (Ed.), Immune Responses in Parasitic Infections, vol. III. Protozoa. CRC Press, Boca Raton, FL, pp. 183–222.
9. Duh, D., Petrovec, M., Avsic-Zupanc, T., **2001**. Diversity of Babesia Infecting European sheep ticks (Ixodes ricinus). J. Clin. Microbiol. 39, 3395–3397.
10. Duh, D., Petrovec, M., Avsic-Zupanc, T., **2005**. Molecular characterization of human pathogen Babesia EU1 in Ixodes ricinus ticks from Slovenia. J. Parasitol. 91, 463–465.
11. Eberhard, M.L., Walker, E.M., Steurer, F.J., **1995**. Survival and infectivity of Babesia in blood maintained at 25 C and 2–4 C. J. Parasitol.81, 790–792.

12. Krause, P.J., Spielman, A., Telford 3rd, S.R., Sikand, V.K., McKay, K., Christianson, D., Pollack, R.J., Brassard, P., Magera, J., Ryan, R., Persing, D.H., 1998. Persistent parasitemia after acute babesiosis. N. Engl. J. Med. 339, 160–165.
13. Krause, P.J., Telford, S.R., **1999**. Babesiosis. In: Gilles, H.M. (Ed.), Protozoal diseases. Arnold, London, pp. 236–248. Krause, P.J., Lepore, T., Sikand, V.K., Gadbaw Jr, J., Burke, G., Telford
14. 3rd, S.R., Brassard, P., Pearl, D., Azlanzadeh, J., Christianson, D., McGrath, D., Spielman, A., 2000. Atovaquone and azithromycin for the treatment of babesiosis. N. Engl. J. Med. 343, 1454–1458.
15. Krause, P.J., McKay, K., Gadbaw, J., Christianson, D., Closter, L., Lepore, T., Telford 3rd, S.R., Sikand, V., Ryan, R., Persing, D., Radolf, J.D., Spielman, A., **2003**. Increasing health burden of human babesiosis in endemic sites. Am. J. Trop. Med. Hyg. 68, 431–436.
16. Krause, P.J., Daily, J., Sam, R., Telford 3rd, S.R., Vannier, E., Lantos, P., Spielman, A., **2007**. Shared features in the pathobiology of babesiosis and malaria. Trends Parasitol. 23, 605–610.
17. Krause, P.J., Gewurz, B.E., Hill, D., Marty, F.M., Vannier, E., Foppa, I.M., Furman, R.R., Neuhaus, E., Skowron, G., Gupta, S., McCalla, C., Pesanti, E.L., Young, M., Heiman, D., Hsue, G., Gelfand, J.A., Wormser, G.P., Dickason, J., Bia, F.J., Hartman, B., Telford 3rd,
18. S.R., Christianson, D., Dardick, K., Coleman, M., Girotto, J.E., Spielman, A., **2008**. Persistent and relapsing babesiosis in immunocompromised patients. Clin. Infect. Dis. 46, 370–376.
19. Swanson, S.J., Neitzel, D., Reed, K.D., Belongia, E.A., 2006. Coinfections acquired from Ixodes ticks. Clin. Microbiol. Rev. 19, 708–727.
20. Telford 3rd, S.R., Gorenflot, A., Brasseur, P., Spielman, A., **1993**. Babesial infection in human and wildlife. In: Kreier, J.P. (Ed.), Parasitic Protozoa, vol. 5. Academic Press, San Diego, CA, pp. 1–47.
21. Telford 3rd, S.R., Goethert, H.K., **2004**. Emerging tick-borne infections: rediscovered and better characterized, or truly ‘new’? Parasitology 129, 301–327.