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Review

Tick-Borne Diseases—Still a Challenge: A Review

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Abstract: Tick-borne diseases account for a large proportion of vector-borne illnesses. They include, for example, a variety of infections caused by bacteria, spirochetes, viruses, rickettsiae, and protozoa. We aim to present a review that demonstrates the connection between the diagnosis, treatment, prevention, and the significance of certain emergency tick-borne diseases in humans and their clinical–epidemiological features. This review covers three diseases: anaplasmosis, ehrlichiosis, and babesiosis. The emergence of ehrlichiosis and anaplasmosis is become more frequently diagnosed as the cause of human infections, as animal reservoirs and tick vectors have increased in numbers and humans have inhabited areas where reservoir and tick populations are high. They belong to the order Rickettsiales and the family Anaplasmataceae, and the clinical manifestations typically coexist. Furthermore, prompt diagnosis and appropriate treatment are critical to the patient's recovery. Similar to malaria, babesiosis causes hemolysis. It is spread by intraerythrocytic protozoa, and the parasitemia dictates how severe it can get. Left untreated, some patients might have a fatal outcome. The correct diagnosis can be difficult sometimes; that is why an in-depth knowledge of the diseases is required. Prevention, prompt diagnosis, and treatment of these tick-borne diseases depend on the understanding of their clinical, epidemiological, and laboratory features.

Keywords: tick borne; anaplasmosis; ehrlichiosis; babesiosis; diagnosis; treatment

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1. Introduction

Tick-borne infections are very important for both health and the economy since they are a large proportion of vector-borne diseases. They comprise a range of infections caused by bacteria, spirochetes, viruses, rickettsiae, and protozoa. We will review three tick-borne diseases: anaplasmosis, babesiosis, and ehrlichiosis and their course in humans. In addition, we aim to illustrate the relationship between the clinical–epidemiological aspects of those emergency tick-borne diseases and their proper diagnosis, treatment, prevention, and significance.

The family Anaplasmataceae is classified in the order Rickettsiales and currently contains five genera and two candidate genera of obligate intracellular bacteria. Four of the genera contain members that are known to infect humans: *Anaplasma*, *Ehrlichia*, *Neorickettsia*, and *Neoehrlichia mikurensis* [1]. Among the abovementioned, *Anaplasma* and *Ehrlichia* are currently two of the most significant emerging tick-borne pathogens. Correspondingly, the ongoing climate and socioeconomic transformations have led to a wide distribution and abundance of arthropods and related illnesses. The data elucidate that, from 2010 to 2018, there was a roughly 12-fold rise in reported cases in the USA [2]. Over the past few decades, the number of these reports has progressively increased, especially in Asia and a few central and northern European countries [3,4]. *Amblyomma americanum* and *Ehrlichia chaffeensis* tick populations have been linked to a northward shift in human ehrlichiosis (HME) cases in the United States [5].

Rickettsial diseases are difficult to diagnose early on because they are typified by an enigmatic febrile state. Pancytopenia is a common laboratory finding associated with

HME early in the illness. About 60–70% of patients have a mild to moderately decreased leukocyte ratio and a significant decrease in lymphocytes [6–9]. Fifty percent of patients experience anemia within two weeks of the illness [8–10]. It is crucial to note that, during convalescence, the majority of patients see a significant increase in their lymphocyte count. This is primarily determined by the activation of γδT-cells. This results in both relative and absolute lymphocytosis [11]. One of the pathognomonic signs of HME is significant thrombocytopenia, which is often found in about 70–90% of patients. About 90% of patients have mild or moderate levels of hepatic cytolysis, with bilirubinemia and increased alkaline phosphatase levels. Up to half of adult patients and 70% of pediatric patients have hyponatremia [9,10,12]. HGA rash is uncommon, noted in less than 10% of patients, compared to HME [13–16]. HGA tends to be a less severe illness than HME.

Doxycycline is the antibiotic of choice for treating ehrlichiosis, anaplasmosis, and all other rickettsial infections. It is approved for patients of all ages, including those under the age of eight. If a patient does not respond to doxycycline, other illnesses resistant to it should be considered in the differential diagnosis. The suggested course of treatment and dosages is 100 mg every 12 h for adults, whereas youngsters under 45 kg (100 lbs.) should take 2.2 mg/kg twice daily. The American Academy of Pediatrics Committee on Infectious Diseases and the Centers for Disease Control and Prevention both endorse the usage of doxycycline as a regular treatment for children who may have rickettsial illness. Short courses of doxycycline (approximately 5–10 days) did not cause any significant adverse reactions, according to a recent study. Alternative antibiotics may be considered in cases of severe doxycycline intolerance, allergy, or pregnancy. Although it has not been tested as a substitute treatment in a clinical situation, rifampin seems to be effective against *E. chaffeensis*. In cases of a tick bite, antibiotic prophylaxis is not recommended [17–19].

HME can be lethal in immunocompetent patients and presents as a multisystem illness akin to toxic or septic shock syndrome [20–22]. Manifold research studies have documented a correlation between the administration of sulfonamide antibiotics and severe *Ehrlichia* symptoms [23,24], although it is unclear whether this statement is accurate. Long-term immunity following a sporadic infection may not always be kept, as there have been occasional reports of laboratory-confirmed reinfections with *A. phagocytophilum*. As a result, people residing in endemic regions where they might encounter infected ticks must take extra precautions to prevent tick bite exposure [14,25]. Avoiding tick bites is one way to prevent tick-borne diseases and removing ticks right away is still the best course of action. People residing in endemic areas ought to wear light-colored clothing when they go outside so that they can see ticks crawling on them [26]. Adults who are highly susceptible to tick bites should treat the exposed areas of skin with chemo-prophylactic repellents, such as DEET (n, n-diethyl-m-toluamide), which deters tick biting. After leaving possibly tick-infested regions, people should thoroughly check their body, hair, and clothing for ticks and remove any that are attached right away. If ticks are attached to the host for 4–24 h, they are more likely to transmit *Ehrlichia* and *Anaplasma* [26–28]. So far, there are no prophylactic measures or vaccines available.

The third infection under consideration is human babesiosis. Caused by intraerythrocytic parasites of the genus *Babesia*, it is a disease akin to malaria. It bears the name of Victor Babes in honor of the European pathologist and microbiologist. Initially, he was the one who identified and detailed the causative agent [29]. The first documented case of human babesiosis occurred in Croatia, then part of Yugoslavia in 1956. It was believed that *Babesia divergens* (*B. divergens*) was the most likely causal agent [30]. These days, 19 European nations routinely report cases of human babesiosis. As well as cases of human babesiosis with babesial pathogens, *Babesia venatorum*, formerly called *EU1*, has been reported in Italy, Germany, Sweden, and Austria. Cases with isolated *Babesia microti* (*B. microti)* have also been presented in Germany [31].

2. Anaplasmosis

Generally, anaplasmosis is spread by tick bites; in Europe, the main vector is *Ixodes ricinus*, also known as the sheep tick or castor bean tick; in the eastern United States, it is *Ixodes scapularis*, also known as the deer tick or black-legged tick; in the western United States, it is *Ixodes pacificus*, also known as the western black-legged tick; and in Asia, it is *Ixodes persulcatus*, also known as the taiga tick [32]. Although its efficacy is low, these ticks can transmit the bacteria to their offspring through transovarial transmission, whereas transstadial transmission is imperative in sustaining *A. phagocytophilum* within its endemic cycles [33–35]. Ticks contract the pathogen when feeding on an infected host. Ruminants and the white-footed mouse (*Peromyscus leucopus*) are common reservoirs of the infection. Other animals, besides horses, that can serve as reservoirs are dogs, domestic or wild ruminants (certain strains), hedgehogs, and wild boars [36,37].

In line with the nymphal and adult stage activity of *Ixodes scapularis* ticks, the disease exhibits a seasonal pattern, with prominent peaks from June through November, correlated with outdoor activities [38]. Moreover, it has been observed that the geographical distribution of *Ixodes* ticks is increasing in latitude and altitude [39], covering a tremendous amount of territory in continental and Atlantic Europe. The fact that Ixodes ticks commonly co-infect other organisms is another crucial aspect of them. Researchers have found that up to 36% of patients with serologic evidence of *A. phagocytophilum* infection also have positive serology for either *Babesia microti* or *Borrelia burgdorferi* infection [40–43]. It has been documented that ticks can carry infections with multiple pathogens concurrently. To illustrate that, publications about co-infections with Lyme disease and tick-borne encephalitis (Powassan and deer tick viral encephalitis) have been reported [44]. It is not yet known whether such concurrent infections will drive increased severity, prolonged duration of illness, or more frequent and severe sequelae [45]. Apart from tick bite transmission, infections among humans have followed blood transfusions [46–48]. In addition, nosocomial exposure via direct contact with blood or respiratory secretion from a severely ill patient with HGA was suspected in China [49], but this assertion is still insufficient [50]. At present, there are an abundance of data that illustrate the pathogen as a burgeoning health issue due to global warming [51] and anthropogenic influence [52]. For instance, the announced annual report has an upward trend rising over a quarter in the global prevalence of the illness for the 50-year study period [53].

An epidemiological study indicates that seroprevalence in Europe ranges from about 8.3% to 31%. The disparity between the high percentage of seroprevalence and recognized symptomatic cases can be attributed to serological cross-reactivity, which may result in an incorrect interpretation of the seroprevalence ratio [54], a large percentage of asymptomatic cases [55], or inadequate diagnosis.

Anaplasma phagocytophilum has been known to cause disease among domestic and wild animals for decades. In the 20th century, in Scotland, an experiment with an ill sheep living on pastures was conducted. During the observation, the animal was tick-infested and later fell ill with a fever of unknown origin, which was named louping-ill (LI) [56]. The disease was temporarily termed "tick-borne fever" (TBF), and the cause was known to be in the class of Rickettsia. At present, the name TBF still refers to an infection in domestic ruminants in Europe. Its current name originates from the Greek word "an", which means "without", and "plasma", "anything formed or molded" [57]. The first case of human granulocytic anaplasmosis (HGA) in the USA dates to 1990, while in Europe (Slovenia), a human diagnosis was initially made seven years later. The patients had a history of tick bite exposure and experienced a severe febrile illness [58–60].

Anaplasma phagocytophilum belongs to the family Anaplasmataceae, the order Rickettsiales, and the class Alphaproteobacteria [53]. This small, obligatory, Gram-negative intracellular bacterium forms morulae, the histopathological hallmark of the disease. Furthermore, it favors myeloid or granulocytic cell growth [43]. The host is first exposed to the infection through a tick bite; after that, the bacteria proliferates within the cytoplasmic vacuoles of polymorphonuclear cells and travels to the spleen and bone marrow. The

bacterium is typically found in neutrophils in the peripheral blood and tissues, where it alters the progenitors of myeloid and monocytic cells. Moreover, proinflammatory reactions brought on by *Anaplasma* in neutrophils cause the degranulation and deactivation of neutrophils as well as the release of cytokines. IL12, IFN-gamma, and IL-10 are the primary cytokines that cause persistent tissue damage. They, thereby, inhibit neutrophils from mounting a potent defense against microorganisms. In addition, the fusion of lysosomes is restricted, and signaling pathways responsible for respiratory bursts are blocked. In addition, *Anaplasma* may affect the regulation of phagocyte oxidase and cause apoptosis, incompetent binding, and transmigration of activated endothelium [43].

Confirmation of the etiological diagnosis of human granulocytic anaplasmosis is achieved using several methods. These include serologic, microscopic identification of characteristic morulae in peripheral blood, detection of nucleic acid by PCR, immunohistochemistry, or culture [43]. Morulae may be found in 25% to 75% of the microscopic samples from patients who have not proceeded with antibiotic therapy. The sensitivity of this diagnostic method is substantial during the first week of infection [61] but dramatically decreases within 24–72 h after initiation of doxycycline [62]. Although SungimChoia, Young-Uk Chob, and Sung-Han Kima [63] presented a case report of a patient with a 5-day illness history and empirical treatment with doxycycline [18]. The culture of *A. phagocytophilum* is time-consuming and thus not routinely available, whereas PCR is more sensitive, highly specific, and time-saving. Additionally, serological tests are widely used to confirm the presence or absence of IgM and IgG antibodies against rickettsia [64]. Human granulocytic anaplasmosis has an incubation period of 1 to 2 weeks and is characterized mostly by a febrile condition. The clinical symptoms range from asymptomatic infection to a fatal outcome [65]. The most common symptoms include fever, chills, sweating, myalgia, arthralgia, gastrointestinal symptoms from the upper tract, and rarely rashes. In contrast, the central nervous system (CNS) is involved rarely, presenting as meningoencephalitis. On the other hand, peripheral nervous system (PNS) involvement includes manifestations such as plexopathy, cranial and facial nerve palsies, and demyelinating polyneuropathy [66–68]. Cerebral infarction [69], seizures, orchitis, glomerulonephritis, myositis with severe rhabdomyolysis, Sweet's syndrome, and hemophagocytic lymphohistiocytosis (HLH) are sporadic signs [66,70–78]. Characteristically, the severity of the disease depends on the patient's age group, concomitant conditions, and the initiation of the treatment. Severe outcomes and hospitalization have been addressed in over a third of the patients. If untreated, manifestations such as respiratory and renal failure, gastrointestinal bleeding, and liver impairment may occur in about 3% of the cases [79].

Recent data indicate that immunosuppressed individuals, such as transplant patients, do not seem to exhibit different clinical signs of anaplasmosis compared to non-transplant recipients. Additionally, favorable outcomes following antibiotic treatment have been reported in these cases [72,77,78].

Paraclinical symptoms of the illness include leukopenia, anemia, thrombocytopenia, and hepatic cytolysis. Furthermore, neutropenia with a left shift and mild lymphocytosis can also be seen [13,80–82]. Moreover, hyperferritinemia and proinflammatory cytokine release have been marked as risk factors for a severe outcome of Anaplasmosis. For those patients with central nervous system manifestations, the CSF (cerebrospinal function) analysis shows lymphocytic pleocytosis and steady protein elevation [80,83].

A. phagocytophilum, as a rickettsial pathogen, is known to be a persistent microorganism in mammalian hosts. However, this characteristic may vary depending on the specific variants of the bacterium involved [38].

3. Human Monocytotropic Ehrlichiosis

Ehrlichia is a genus in the Ehrlichiaceae family, order Rickettsiales, class Alphaproteobacteria. The genus consists of two species that cause illness among humans. *Ehrlichia chaffeensis*, which causes human monocytic ehrlichiosis (HME), and *Ehrlichia ewingii*, associated with *Ehrlichia ewingii ehrlichiosis*. In addition, pathogens with mostly veterinary

significance that rarely infect humans are *Ehrlichia canis* and *Ehrlichia ruminantium.* A recently described EMLA (*Ehrlichia muris*-like agent) and *E. muris eauclairensis* have also been associated with human disease [84].

Ehrlichia is a Gram-negative obligate intracellular coccobacillus. As a non-motile bacteria, it resides and cultivates in cytoplasmic vacuoles, composing aggregates of bacteria called morulae. Under light microscopy, morulae resemble intracytoplasmic inclusions that stain dark blue or purple with Romanowsky-type stains and look like mulberries. In Latin, the word "morus" comes from morum and means mulberry [85]. Ehrlichial morulae have been identified in numerous fluids and tissues, such as blood, bone marrow, hepatic sinusoids, splenic cords, lymph nodes, and cerebrospinal fluid (CSF) macrophages.

Ehrlichia's vectors of transmission are North American ticks from the species lone star tick (*Amblyomma americanum*), the American dog tick (*Dermacentor variabilis*), as well as Ixodes scapularis (black-legged tick). The pathogen can be transmitted transstadially (through their life stages) but not transovarially. In addition to humans, other hosts include domestic and wild animals such as dogs, cattle, sheep, goats, rodents, and deer. Other possible rare ways of transmission are blood transfusions and organ transplants.

The annual incidence ratio of human ehrlichiosis has been statistically confirmed to be 3 to 5 per 100,000 in endemic territories in the USA [86]. Also, in 2019, the Centers for Disease Control and Prevention stated that about 50% of the cases of ehrlichiosis in the USA were diagnosed in just four states (Missouri, Arkansas, North Carolina, and New York). Moreover, since 2009, more than 115 cases of ehrlichiosis with the causative agent *E. muris eauclairensis* have been announced in the Upper Midwest. In contrast, in Europe, the incidence rate is significantly low since less is known about Ehrlichiosis distribution [87–89]. Presumably, in Europe, HGE is not reported as often as in other parts of the world because of its less severe course. Thus, it is frequently underdiagnosed.

In HME, clinical manifestations appear in 5 to 14 days after the tick bite. The illness usually presents itself with a febrile illness characterized by myalgia, headache, nausea, vomiting, diarrhea, anorexia, and rash. Generally, every third patient experiences a rash, which is more common among those infected with *E. chaffeensis* and is present more frequently in children compared to adults, in whom it is often found in patients with HIV [90]. The eruption occurs mainly up to 5 days after the febrile condition initiates and can be maculopapular or petechial [91]. Adults with serious disease experience diarrhea, lymphadenomegaly, and confusion, while the pediatric population experiences edema on the extremities. Moreover, complications occur in between 9 and 17% of the cases. For instance, ARDS (acute respiratory syndrome), DIC (disseminated intravascular coagulation) syndrome, renal failure, CNS manifestations (CSF lymphocytic pleocytosis and increased protein levels), and others. *Ehrlichia chaffeensis* may lead to hemophagocytic lymphohistiocytosis (HLH) [18,40,92–100]. Researchers report that, relatively, one to three in ten infections have been reported in immunocompromised patients, which is why *E. chaffeensis* acts as an opportunistic parasite [90,101,102].

Etiological diagnosis can be obtained with several methods. The most widely used one is serology because it is a cost-effective and relatively fast method, but it can give false positive or negative results due to cross-reactivity reactions and usually comes back negative for most of the tests in the first week of the disease [103]. Another example is the visualization of morulae and staining method, a rapid and seldomly used confirmatory practice [104–108]. Morulae are typically seen in less than 5% of the leukocytes. A case series documented individuals for whom morula visualization was an independent diagnostic sign. A culture or PCR confirmation is approximately one-third of all for those first identified with morulae in the blood [104,106,109].

PCR techniques have become more commonly used to detect DNA from *Ehrlichia* spp. in whole blood, CSF, and serum. When serologic testing is still negative, an acute-phase whole-blood sample from *E. chaffeensis* patients can often yield positive results by PCR [104]. A lab procedure that can process cell culture is necessary for the separation of *Ehrlichia species* from blood, CSF, and other tissues. Some cultures have shown signs of morulae as

early as two days after inoculation, while in others, primary isolation has taken a much longer time [105,106,110].

4. Human Babesiosis

Nowadays, human babesiosis has been reported in 19 European countries. Cases of human babesiosis with a proven other member of the genus *Babesia*—*Babesia venatorum* (*B. venatorum*), formerly called *EU1*—have been described in Italy, Germany, Sweden, and Austria. Cases with isolated *Babesia microti* (*B. microti*) have also been described in Germany [30].

Over 100 species of the genus *Babesia* have been reported but only a few are pathogenic to humans—*B. microti*, *B. divergens*, *B. duncani*, *B. venatorum*, and an as-of-yet unnamed strain named *MO*-1 [111,112]. In North America, the most common causative agent is *B. microti*, whose vector is *I. scapularis*. It is widespread in the midwestern United States [113]. The second most common species in North America is *B. duncani*. Cases of human babesiosis with *B. duncani* as the proven causative agent have been reported along the Pacific coast of the United States and Canada [113,114]. There are various studies suggesting that the vectors of *B. duncani* are the black-legged tick, *I. scapularis;* the western black-legged tick, *I. pacificus;* and the winter tick, *Dermacentor albipictis* [113,115,116]. In Europe, the most common causative agent of human babesiosis is *B. divergens*, whose vector is *I. ricinus*. In addition to *B. divergens*, *I. ricinus* also carries *B. venatorum* and *B. microti*. In South Asia, *B. microti* is transmitted by *Ixodes ovatus* Neumann, while cases of *Babesia crassa* and *B. venatorum* have been reported from China, probably transmitted by *I. persulcatus* [117]. People of any age and sex can be affected by human babesiosis. It is most severe in patients over 40 years of age who are immunosuppressed or splenectomized. A different phenomenon of disease transmission has also been described in the USA—in blood transfusions with infected blood [117].

Babesia belong to the phylum: Apicomplexa, the class: Sporozoa, the order: Piroplasmida, the family: Babesiidae, and the genus: *Babesia* [118]. *Babesia* are divided according to their size into large babesia (2.5–5)—*B. bigemina*, *Babesia caballi*, *Babesia canis*, etc.—and small babesia (1.0–2.5)—*B. bovis*, *Babesia gibsoni*, *B. microti*, *Babesia rodhaini*, etc. [119]. The biological cycle of babesia occurs in two hosts. Sexual reproduction takes place in ticks and the asexual phase happens in vertebrates. The biological stages are described as follows: in animals—schizogony, erythrocyte cycle: trophozoites—small babesias of 1–2.5 mt and large babesias of 2.5–5 mt (ring shaped), merozoites, gametes. In the tick, it is described as follows: gametogonia (sexual reproduction)—in the stomach of the tick; ookinetes and sporogonia—formation of sporozoites in the salivary glands. The infected ticks inoculate the host with their saliva while feeding, after which approximately sporozoites penetrate erythrocytes. Simple fission (schizogony) follows, producing merozoites. They lyse infected cells and penetrate new erythrocytes. Some of the trophozoites do not reproduce in the blood but differentiate into male and female gametes [120].

Following a tick bite, *Babesia* enters the capillary blood of the infected individual, targeting the erythrocytes. Unlike *Plasmodium* species, which enter the erythrocytes directly, *Babesia* begins to mature and grow [120]. The initial stages of the cycle closely resemble those of *Plasmodium* species, appearing as ring parasites. This is followed by a budding process in which they replicate and form an “eight”, with budding able to recur, resulting in the production of a tetrad known as a “Maltese Cross”. Upon reaching the merozoite stage, the parasites exit the erythrocyte cells, causing their lysis, and seek out new cells to infect [121].

The disease can vary in severity depending on various factors—the age of the patient, their immunological status, the type of parasite, etc. The disease is most severe in neonates and in all immunocompromised patients, especially in asplenic patients. It is not known how long it takes for the infection to be transmitted from tick to human; in white-footed mice, it has been found to take 36 to 54 h [122]. The incubation period for tick-borne transmission is 1 to 4 weeks, and when the infection results from hemotransfusion, the

incubation period is up to 6 weeks [123]. *Babesia* possess mechanisms to evade the immune response, which often results in the persistence of infection in healthy individuals, who are most often asymptomatic; this is particularly characteristic of *B. microti*. In case of infection with *B. microti* in healthy individuals, the disease may proceed asymptomatically; in mild parasitemia <4%, the most common symptoms include myalgia, fever, chills, headache, vomiting, and diarrhea. In high parasitemia (>10%) [124,125], complications such as acute respiratory distress syndrome, renal failure, shock, disseminated intravascular coagulopathy, and congestive heart failure may occur. In up to 10% of hospitalsed patients, it ends up being lethal, and if the infection is the result of chemotherapy, this percentage reaches 20% [126]. Infections with proven-causative *B. divergens* can run from mild to severe. Parasitemia in different cases varies from 0.29% [127] to 20% [128] in the mild course of the disease, with the symptoms being flu-like arthromyalgia, fever, headache, and chills, and in the more severe course, hemolytic anemia, jaundice, renal failure, hemoglobinuria, vomiting, and abdominal pain may develop and may end fatally. There have been five reported cases in Europe of infection with the proven causative agent *B. venatorum*, all described in patients over 50 years of age with severe immunosuppression. It can run again from mild to severe. The symptoms reported include shortness of breath, progressive weakness, intermittent episodes of fever, jaundice, thrombocytopenia, hemoglobinuria, and acute renal failure. Parasitemia ranges from 1.3% to 30% [129]. A study in China found 48 of 2912 seropositive cases, demonstrating that infection with *B. venatorum* infection is milder in immunocompetent patients compared to *B. divergens* infection [130].

In the past, ignorance of the existence of *Babesia* ssp. and that they can cause disease in humans led to many misdiagnoses. There are still cases in which babesiosis is proven postmortem. Episodes of fever accompanied by hemolytic anemia and a positive Coombs test, together with elevated procalcitonin levels and a history of a tick bite, travel to babesiosis-endemic countries, or blood transfusion necessitate thinking in the direction of a diagnosis of babesiosis [131,132].

The gold standard for proof of babesiosis is the detection of the parasite in a blood smear stained by the Giemsa or Romanowsky method. The parasitemia is small in the initial stages of the disease, necessitating the collection of a series of blood samples, evaluating over 300 fields of view. Differential diagnosis with malaria is important. It has applications in research because it is a laborious and lengthy process in which animal species are infected with parasites—*Babesia divergens*, *B. microti,* and *B. duncani*—and the presence of parasitemia in their blood is monitored for up to two months [131]. The indirect immunofluorescence assay is the most commonly used serological test method. IgG—at borderline titers of 1:32 to 1:160, specificity > 90%, and sensitivity > 88%—is found. In the course of infection, titers of >1:1028 may be detected, subsequently decreasing to 1:64. A disadvantage of IgG testing is that it cannot differentiate whether the infection is axial, subacute, chronic, or has already passed. IgM indicates acute infection but can give false positive results; this requires a two-stage testing process in which individuals with a positive IgG Ab are tested for IgM Ab [132,133]. Immunofluorescence assays are inaccurate, non-specific, variable, and often false positive in patients with rheumatologic diseases and those with similar infectious diseases such as malaria and toxoplasmosis [134]. Molecular biology tests have the highest sensitivity and are used in patients with low parasitemia, and it has been shown that real-time PCR can detect up to 20 genomic copies in 1 microliter of blood. Most commonly, 18sRNA is used for the detection of *Babesia* spp. [135].

Choosing the right therapy and its duration depends on the type of parasite, the immunological status of the patient, the severity of the disease, and a number of factors. A combination of antiparasitic and antibiotic medication is advisable. In case of infection with *B. microti,* a standard combination is used—atovaquone/azithromycin [136], a study was conducted that proved that the combination of quinine plus clindamycin has the same effect, but the risk of more frequent and more severe side effects increases [137]. Cases of asplenic patients infected with *B. divergens* are regarded as emergencies, as a large proportion of them end lethally [4]. Significant improvement in the patient's condition is reported from

the administration of a combination of clindamycin and quinine for 7 to 10 days [138]. In infection with *B. venatorum,* treatment with clindamycin in combination with quinine, followed or not by treatment with atovaquone and azithromycin, dramatically improves disease outcome [139].

5. Conclusions

An increasing number of cases of vector-borne diseases are being reported worldwide, with a large proportion of these being associated with tick-borne diseases. This can be attributed to the increased tick population in the Northern Hemisphere associated with ecological changes. Urbanization and the cosmopolitan lifestyle of modern people are the other two factors that determine the prevalence of tick-borne diseases. The diseases we have described were first reported in humans in the last century, so there are still no reliable, rapid, and accessible methods available for their diagnosis. Knowledge of their epidemiology, mode of transmission, clinical characteristics, and effective therapy is essential for the health worker. The diseases under consideration are socially important, as their symptoms may initially be non-specific, most often influenza-like, but can very quickly develop into clinical symptomatology. Left untreated, some patients have a fatal outcome. A series of measures are needed to increase the knowledge of health professionals, develop innovative methods for their detection, and determine their susceptibility to drugs intended for their eradication. Some screening programs, such as the testing of blood products for the presence of infectious agents and the development of vaccines, are also yielding positive results.

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