

## Hematological and biochemical determinants of anemic syndrome in animals with babesiosis: A review of current data

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A review of *Babesia* infection in dogs and other animals is presented, including the life cycle, epidemiology, hematological and biochemical changes, oxidative stress, immune response, clinical manifestations, diagnostic challenges, and treatment strategies. Babesiosis is a multifactorial disease caused by intraerythrocytic protozoa of the genus *Babesia*, primarily transmitted by ticks. Species such as *B. canis*, *B. vogeli*, *B. gibsoni*, and *B. rossi* differ in pathogenicity and geographic distribution. Pathogenesis involves massive hemolysis, systemic inflammation, hepatic and renal dysfunction, metabolic disorders, and oxidative stress, leading to anemia, thrombocytopenia, changes in leukocyte composition, and organ damage. Biochemical markers include elevated ALT, AST, ALP, bilirubin, BUN, creatinine, and oxidative stress markers (MDA, LDH) with decreased antioxidant enzymes (SOD, catalase, PON-1). Acute phase proteins (SAA, CRP) and antibody titers correlate with severity of infection and prognosis. Microscopy and serology have diagnostic limitations, while molecular methods (PCR, qPCR, LAMP) provide higher sensitivity. Clinical management requires a combined approach: specific antiprotozoal therapy, supportive care (infusions, transfusions), hepatoprotection, and correction of protein-energy balance. Comparative data for dogs, horses, and wild animals demonstrate common pathogenetic mechanisms, emphasizing the role of wild reservoirs and expansion of the vector range in the spread of the disease. Integration of hematological, biochemical and immunological markers improves early diagnosis, monitoring and prognostic assessment, especially in regions at risk of vector-borne transmission.

**Keywords:** *Babesia*; dogs; hemolytic anemia; oxidative stress; acute phase proteins; transmissible diseases; molecular diagnostics; supportive care; epidemiology.

### Introduction

The genus *Babesia* includes over 100 species, but the most clinically important for dogs are *Babesia canis* (with subspecies *B. canis canis*, *B. canis vogeli*, *B. canis rossi*) and *Babesia gibsoni*. They differ in virulence, distribution and vectors. Thus, *B. canis canis* is the main pathogen in Eastern and Central Europe, in particular in Ukraine, while *B. canis vogeli* dominates in Mediterranean and tropical countries, *B. canis rossi* is limited to Africa and is known for its most severe course. *Babesia gibsoni* is widespread in Asia and occurs in the Americas (Seleznova, 2020; Drehmann, 2020; Rube, 2020; Dwuznik-Szarek, 2021; Daněk, 2022; Pawelczyk, 2022).

The ecology of babesia is closely related to the range of ticks – the main vectors. The pathogens are maintained in natural foci due to transovarial and transstadial transmission in ticks of the genera *Dermacentor*, *Rhipicephalus*, *Ixodes* and *Haemaphysalis* (Drehmann, 2020; Dwuznik-Szarek, 2021; Daněk, 2022). The reservoir hosts are wild canids (wolves, jackals), as well as small mammals, which ensures the stability of the parasite circulation in nature.

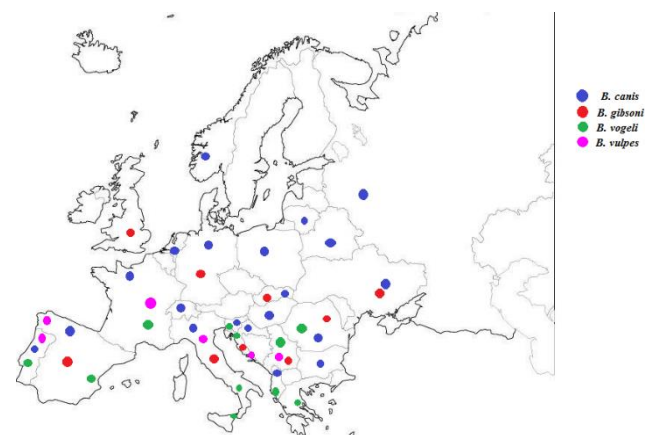
The global distribution of different *Babesia* genotypes demonstrates clear geographical segregation (Seleznova, 2020; Drehmann, 2020; Rube, 2020; Dwuznik-Szarek, 2021; Daněk, 2022; Pawelczyk, 2022) (Fig. 1):

- Europe (Central and Eastern) – *B. canis canis*;
- Mediterranean and tropics – *B. canis vogeli*;
- Africa – *B. canis rossi*;
- Asia, America – *B. gibsoni*.

In Ukraine, *B. canis canis* predominates, which correlates with the distribution of the *Dermacentor reticulatus* tick, especially in Polesie and the Forest-Steppe (Dubova, 2005b; Fasolya, 2007).

The phylogenetic analysis presented in Figure 2 demonstrates the relatedness of the main *Babesia* species that infect dogs. The tree is constructed based on a portion of the 18S rRNA gene aligned using CLUSTAL W and analyzed by Neighbor-Joining with node confidence estimated using 1,000 bootstrap replicates. The main clades include *B. canis vogeli*, *B. canis canis*, *B. canis rossi*, *Babesia* sp. and

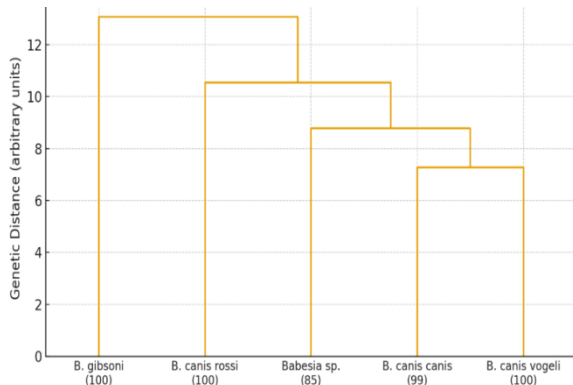
*B. gibsoni*, with bootstrap support of 100, 99, 85 and 71 for the respective nodes (Hirata, 2022). The results demonstrate a clear genetic segregation of the species, allowing comparison of local isolates with globally known sequences and highlighting evolutionary relationships between pathogens clinically relevant to dogs in Europe, particularly in Ukraine. The use of such phylogenetic trees helps to understand the genetic diversity and potential routes of *Babesia* spread in canine populations.



**Fig. 1.** Geographic distribution of *Babesia* species in dogs across Europe: data for Ukraine are included based on clinical findings; *B. canis* identified via blood smear and *B. gibsoni* detected by serological testing; in other European countries, species identification was primarily conducted using molecular analyses (adapted from Solano-Gallego & Baneth, 2011)

Babesiosis is one of the most common transmissible protozoal diseases in the world and in Ukraine, which has important veterinary-sanitary, economic and clinical significance (Dubova, 2005a; Dubova, 2005b; Goralska, 2024). According to epidemiological data (Dubova, 2005b; Fasolya, 2007), the incidence among dogs is con-

stantly increasing. Endemic foci of protozoa in Ukraine, in particular, are Zhytomyr region, where the share of protozoal invasions among all sick dogs reaches 26.4%, and during the peak of seasonal activity – 62% (Dubova, 2005a, 2005b; Fasolya, 2007). Also, according to the thesis of G. I. Golovkova, the epizootic situation regarding canine babesiosis in the territory of the city of Dnipro is unfavorable, accounting for 18.2% of all parasitic diseases. The most dangerous months for the occurrence of invasion are May (23.2%) and September (19.9%) (Golovkova, 2020).



**Fig. 2.** Simplified Neighbor-Joining phylogenetic tree for the main *Babesia* species in dogs with bootstrap support (Hirata, 2022)

The clinical significance of babesiosis is determined, first of all, by the development of hemolytic anemia, which is a key pathogenetic factor in the severity of the disease (Semenko, 2006; Levitskaya, 2020a, 2020b). Hemolysis of erythrocytes causes sequestration of invaded cells in the vessels of the liver, kidneys, intestines, spleen and central nervous system, which leads to impaired microcirculation and tissue hypoxia (Levitskaya, 2020b; Karasová, 2022). As a result, anaerobic glycolysis is activated, lactic acid accumulates, metabolic stress occurs, and toxic protein breakdown products and renal toxins stimulate systemic intoxication (Herrmann, 2015; Levitskaya, 2020b; Mazanny, 2020). An important pathogenetic complication is the development of hepatorenal syndrome, which is accompanied by complex liver and kidney dysfunction, cardiovascular complications, pulmonary edema, damage to the central nervous system and impaired hemostasis (Herrmann, 2015; Karasová, 2022). Morphofunctional changes in one organ affect the state of other systems, which complicates clinical diagnosis and prognosis of the disease (Herrmann, 2015).

The development of modern diagnostic methods has significantly improved the assessment of internal pathology in babesiosis. The use of radiological, endoscopic, ultrasound and computer methods allows visualization of morphological changes in organs (Levitskaya, 2020c). At the same time, laboratory diagnostics of anemic syndrome and complications in babesiosis needs improvement. Limited availability of enzyme immunoassay and polymerase chain reaction complicates early and accurate diagnosis, especially in the acute form of the disease (Levitskaya, 2020b, 2020c). In addition, the dynamics of hematological and biochemical indicators, which can serve as markers of the severity of anemia and the prognosis of complications, have not been studied sufficiently (Semenko, 2006).

Systematic study of hematological and biochemical determinants of anemic syndrome in dogs with babesiosis is relevant. The generalization of current data allows us to assess the effectiveness of etiotropic and pathogenetic therapy, as well as to identify early prognostic markers of liver and kidney damage in the context of hepatorenal syndrome (Herrmann, 2015; Levitskaya, 2020b; Kovalenko, 2021; Goralska, 2024). In Ukraine, there are no comprehensive scientific works that systematically analyze the pathogenesis, diagnostic criteria and approaches to the treatment of anemia in babesiosis, which emphasizes the relevance of conducting a detailed review and generalization of world experience (Semenko, 2006; Karasová, 2022; Goralska, 2024).

The purpose of this review is to systematize current scientific data on hematological and biochemical determinants of anemia syndrome

in dogs with babesiosis, as well as to assess the dynamics of these indicators under the influence of etiotropic and pathogenetic therapy.

Scientific substantiation of the informativeness of early diagnostic markers of the functional state of the liver and kidneys in the context of hepatorenal syndrome and identification of key pathogenetic links of the disease are important tasks of modern veterinary medicine (Semenko, 2006; Karasová, 2022).

## Materials and methods

The aim of this review was to provide a comprehensive analysis of canine babesiosis, focusing on epidemiology, clinical manifestations, hematological and biochemical changes, diagnostic methods, and therapeutic approaches. The literature for this review was systematically selected using electronic databases, including PubMed and Google Scholar, using combinations of keywords such as “*Babesia canis*”, “*Babesia vogeli*”, “*Babesia gibsoni*”, “canine babesiosis”, “tick-borne diseases”, “diagnosis”, “hematology”, “biochemistry”, and “therapy”. In addition, references cited in these publications were analyzed to identify additional relevant studies. The authors also used their own collections of veterinary literature accumulated over many years of research.

The inclusion criteria for the selected studies were peer-reviewed articles, monographs, textbooks, and conference proceedings without restrictions on year of publication, study location, breed, age, or sex of animals. Editorials, commentaries, and publications without primary data were excluded from the review. A total of 64 sources were reviewed, covering Ukrainian and international studies spanning over two decades. Both natural and experimental cases of canine babesiosis were included to provide a comprehensive understanding of the pathogenesis, clinical course, and diagnostic challenges. The review was conducted in several stages. The initial stage summarized the epidemiology of canine babesiosis, including prevalence, vector distribution (particularly *Dermacentor reticulatus*), and the role of wild and domestic reservoir hosts. Particular attention was paid to studies from Europe, Asia and the Middle East, as these regions provide insight into both endemic and emerging foci of infection.

Clinical and laboratory manifestations of infection were then reviewed. Hematological parameters such as red blood cell count, hematocrit, hemoglobin concentration, white blood cell profile and platelet count were assessed, as well as biochemical markers including liver enzymes (ALT, AST, ALP), renal function tests (creatinine, BUN), bilirubin, protein fractions and electrolytes. Oxidative stress markers and acute phase proteins were also included to reflect the complexity of the systemic response to *Babesia* infection.

Diagnostic methods were reviewed, with an emphasis on traditional approaches (blood smear microscopy, clinical hematology) and modern molecular techniques (PCR, qPCR, LAMP). The sensitivity, specificity, advantages and limitations of each method were discussed depending on the stage of the disease, parasite load and clinical manifestations. Serological studies and antibody titer assessment were also reviewed to understand the dynamics of the host immune response and its role in disease progression.

Finally, therapeutic strategies are summarized, including the use of antiprotozoal drugs, supportive care, immunomodulatory interventions and management of complications such as severe anemia, liver or kidney dysfunction and systemic inflammation. A comparative analysis of treatment outcomes, including recovery and mortality rates, was conducted based on both retrospective studies and controlled experimental studies.

This structured approach allowed for the integration of diverse sources and provided a holistic view of canine babesiosis, its pathogenesis and management. The methodology ensured coverage of both global trends and regional specificities, providing a detailed resource for veterinary practitioners, researchers and public health authorities.

## Biology and pathogenesis of the genus *Babesia*

The genus *Babesia* belongs to the phylum Apicomplexa, class Aconoidasida; it is an obligate intracellular hemoparasite of erythro-

cytes of many mammals (dogs, large and small horned animals, horses, rodents, humans) (Vannier, 2020; Djokic, 2021). The modern classification of species in dogs distinguishes at least four key taxa – *B. canis*, *B. rossi*, *B. vogeli* (complex of “large” *Babesia*) and *B. gibsoni* (“small” *Babesia*) – which differ in virulence, geography and vectors (Penzhorn, 2020a; Karasová, 2022; Birkenheuer, 2023). For humans, clinically significant are, in particular, *B. microti* (North America, Europe) (Panti-May, 2020), *B. divergens* (Europe) and others (Vannier, 2020; Bajer, 2022).

The sexual cycle occurs in ticks (Ixodidae) with transovarial and transstadial transmission; asexual schizogonial reproduction occurs in the host's erythrocytes (Vannier, 2020; Djokic, 2021). For *B. canis*, the key vectors in Europe are *Dermacentor reticulatus* and *D. marginatus*; the range of *D. reticulatus* in Central and Northern Europe has expanded in recent years, correlating with the increase in canine babesiosis cases and the emergence of foci outside the traditional distribution areas (Drehmann, 2020; Rube, 2020; Seleznova, 2020; Dwuznik-Szarek, 2021; Daněk, 2022; Pawelczyk, 2022). *B. vogeli* is more commonly associated with *Rhipicephalus sanguineus* s. l., and *B. rossi* with *Haemaphysalis elliptica* in South Africa (Penzhorn, 2020a; Penzhorn, 2020b). Ecological changes in tick fauna and animal movements (travel/import) contribute to autochthonous cases in “new” regions (Helm, 2022; Weingart, 2023).

*Babesia* merozoites use the apical complex (micronemes, rhoptries) for adhesion and invasion of the erythrocyte, form a transient parasitophorous vacuole (which quickly disappears), followed by merogony with the formation of paired/cruciform forms and subsequent cell lysis (Vannier, 2020; Djokic, 2021). The lack of a stable vacuole distinguishes *Babesia* from *Plasmodium* and affects immunopathogenesis and drug access to the parasite (Djokic, 2021). Key mechanisms in dogs and humans include: direct intracellular replication with erythrocyte rupture; immune-mediated hemolysis (opsonization, extravascular destruction in the spleen and liver); oxidative membrane damage and changes in erythrocyte deformability (Djokic, 2021; Zygnier, 2023). Elevated levels of proinflammatory cytokines (TNF- $\alpha$ , IL-6, chemokines) are associated with severe anemia and systemic inflammatory response (SIRS) (Milanović, 2020; Beletić, 2021; Zygnier, 2023). High parasitemia can lead to microcirculatory disorders, disseminated hemostasis, and ischemic organ damage (Dubova, 2005a; Teodorowski, 2021; Zygnier, 2021). In naturally infected dogs with *B. canis*, high parasitemia and host characteristics correlate with SIRS, hypotension, DIC, and acute kidney/liver injury (Milanović, 2020; Beletić, 2021; Goralska, 2024). Autoimmune phenomena, thrombocytopenia, and dysproteinemia (electrophoretic profile changes) have been described (Dantas-Torres, 2020; Tóthová, 2020; Teodorowski, 2021). Severe complications, including atraumatic splenic injury in babesiosis, are possible in humans (Sung, 2021).

Dogs are characterized by hemolytic anemia, hyperbilirubinemia, liver and kidney damage (hepatorenal syndrome), pulmonary changes, pancreatic damage; morphological data confirm microthrombosis, congestion and dystrophic changes of parenchymal organs (Dubova, 2020; Matviychuk, 2020; Zygnier, 2021; Goralska, 2024). Hemostasis disorders can be a consequence of DIC syndrome, as well as specific defects of the coagulation system in severe cases (Dubova, 2005a; Birkenheuer, 2020; Teodorowski, 2021). Infections with “large” *Babesia* (*B. canis*, *B. rossi*, *B. vogeli*) in dogs more often cause acute hemolytic syndrome with severe fever, while *B. gibsoni* often has a subacute/chronic course with persistent anemia, immune complications and relapses (Tóthová, 2020; Karasová, 2022; Birkenheuer, 2023). In Europe, the more severe course is primarily associated with *B. canis* and outbreaks in regions of *Dermacentor* expansion (Drehmann, 2020; Strobl, 2020; Dwuznik-Szarek, 2021; Helm, 2022).

Past infection induces partial, strain-specific immunity; the role of antibodies and cellular responses is mixed, and excessive pro-inflammatory response increases tissue damage (Djokic, 2021; Zygnier, 2023). Co-infections with other transmissible pathogens (e.g., *Dirofilaria repens*, *Borrelia burgdorferi* s. l.) alter hematological indices, immune profile, and may complicate clinical presentation (Bajer, 2022; Wężyk, 2023). In rodent models, *B. microti* affects the course of pregnancy, emphasizing the immunological specificity of patho-

genesis (Tołkacz, 2021). In Central and Northern Europe, an increase in autochthonous cases of *B. canis* in dogs has been recorded, including in areas outside the known range of the vector; genetic diversity of strains in local outbreaks is high (Efstratiou, 2021; Helm, 2022; Pawelczyk, 2022; Weingart, 2023). Pan-European reviews indicate the increasing importance of babesiosis as a zoonosis/anthropozoonosis (for certain species), as well as a veterinary problem that connects animals and humans (Vannier, 2020; Bajer, 2022; Garcia, 2022).

The level of parasitemia, antibody titers and acute phase markers are associated with hematological biochemical abnormalities and severity of the course (Teodorowski, 2021; von Hohnhorst, 2025). The morphology of erythrocytes in babesiosis reflects both a direct cytopathic effect and immune-mediated mechanisms (Dubova, 2005b; Otranto, 2021; Zygnier, 2023).

Thus, the genus *Babesia* is a group of intracellular hemoparasites with a complex development cycle, where sexual stages occur in vector ticks, and asexual reproduction occurs in vertebrate erythrocytes. Pathogenesis is characterized by a combination of direct hemolysis, immune-mediated erythrocyte damage, proinflammatory response, and hemostasis disorders, leading to anemia, multiorgan involvement, and systemic inflammatory response. Species such as *B. canis*, *B. rossi*, *B. vogeli*, and *B. gibsoni* differ in virulence, geography, and vectors, and co-infections and genetic diversity of the parasites complicate the course of the disease, emphasizing the importance of understanding the biology and pathogenesis of *Babesia* for the diagnosis, prevention, and treatment of both animals and humans.

#### Hematological determinants of the anemic syndrome in babesiosis

In canine babesiosis, anemia is polymorphic in type and severity. Hemolytic, regenerative, and aplastic forms of anemia are most commonly observed (Dubova, 2005b; Zygnier, 2023; Goralska, 2024). Hematological changes are characterized by:

1. Decreased hemoglobin (Hb), hematocrit (Ht), and erythrocyte (RBC) levels, reflecting massive hemolysis and red cell depopulation (Dubova, 2005b; Gonmei, 2020).

2. Increased mean corpuscular volume (MCV) and decreased mean corpuscular hemoglobin concentration (MCHC), indicating a regenerative response of the bone marrow (Gonmei, 2020).

3. Impaired reticulocyte pool, indicating compensatory erythropoiesis, and changes in the white blood cell count and thrombocytopenia due to immune complex damage (Gonmei, 2020; Wężyk, 2023).

Pathogenetically, anemia is formed under the influence of several interrelated mechanisms: direct destruction of erythrocytes by the parasite, immune damage through antibodies and complement, oxidative stress and microcirculatory disorders (Zygnier, 2021; Zygnier, 2023). A study conducted in the state of Mizoram (India) showed that infected dogs have a significant decrease in Hb, Ht, RBC and MCHC, an increase in MCV, leukocytes and monocytes, which correlates with the severity of clinical manifestations, including fever, depression and jaundice (Gonmei, 2020). Increased activity of lipid peroxidation (LPO) and a decrease in antioxidant enzymes (SOD, catalase, TAC) contribute to the progression of hemolysis and complicate the regenerative response (Gonmei, 2020). Thus, hematological parameters not only serve as diagnostic markers, but also reflect the severity of pathogenetic processes and the prognosis of the clinical course of babesiosis (Gonmei, 2020; Zygnier, 2023; Goralska, 2024).

A study conducted in Mashhad (northeastern Iran) demonstrated a significant prevalence of *Babesia* spp. among different categories of dogs, including domestic, stray, and shelter dogs (Kafrahi, 2024). PCR-based infection rates were 15.3%, while microscopy detected only 2% of cases, highlighting the need for molecular methods for accurate diagnosis. Sequencing confirmed the presence of *B. vogeli* in large *Babesia* cases with 100% sequence identity. The study also showed that housing factors and age of the dogs had a statistically significant effect on the probability of infection ( $P < 0.05$ ), while gender was not a determinant. Hematological data showed a decrease in hematocrit (Hct) and red blood cell (RBC) counts in infected dogs,

reflecting severe non-regenerative anemia. In some cases, pancytopenia and biochemical abnormalities were observed, including azotemia, hyperphosphatemia, hyperkalemia, hypoglycemia, and hypocholesterolemia, suggesting systemic involvement of the kidneys and liver in the pathogenetic process (Panti-May, 2020; Kafrahi, 2024).

A study of police dogs in Egypt showed similar trends: *B. vogeli* infection, and in some cases co-infection with *Ehrlichia canis*, caused increased levels of oxidative stress and expression of the pro-inflammatory cytokines IFN- $\gamma$  and TNF- $\alpha$  (Zaki, 2021). Infected animals exhibited hematological and biochemical abnormalities that correlated with the severity of clinical manifestations, including lethal outcomes in severe cases. These data confirm the close relationship between the intensity of parasitemia, oxidative stress, and the development of anemia in dogs with babesiosis (Gonmei, 2020; Zaki, 2021).

Similar patterns are observed in sheep infected with *Babesia ovis* in Pakistan (Sajid, 2023). Infected Lohi sheep show a significant decrease in RBC, Hb and Hct ( $P < 0.0001$ ), consistent with classical hemolytic anemia. Minor changes in MCV, RDW, MCH and MCHC reflect compensatory erythrocyte adaptations. Leukopenia observed in infected sheep suggests immune suppression or overstimulation of leukopoiesis. Biochemical changes, including increased blood urea nitrogen (BUN) and total bilirubin, confirm the toxic effects of the parasites on the kidneys and liver (Sajid, 2023).

In racehorses in Erbil province (Iraq), infection with *Babesia caballi* and *Theileria equi* results in microcytic anemia, decreased RBC, Hb, and hematocrit, and increased WBC, lymphocytes, and basophils (Aziz, 2025). Biochemical changes include increased liver enzymes (AST, ALT, ALP) and total bilirubin, as well as decreased total protein, albumin, calcium, and glucose, indicating systemic intoxication and metabolic homeostasis (Eslahi, 2021; Aziz, 2025). A study conducted in Mizoram, India, confirmed that *Babesia gibsoni* is the main causative agent of babesiosis in dogs in this region (Gonmei, 2020). Molecular diagnostics using PCR allowed the detection of infection even at a low incidence (1.25% of all dogs examined). Infected animals exhibited classic clinical signs of babesiosis: fever, exhaustion, depression, jaundice, and lymphadenopathy. Hematological abnormalities included decreased hematocrit, hemoglobin, RBC, and MCHC, as well as total protein and albumin, while MCV, WBC, and monocytes were elevated. Biochemical changes were characterized by elevated BUN levels. Significant oxidative stress abnormalities, including decreased SOD, catalase, and TAC activities and increased lipid peroxidation (LPO), suggest the development of oxidative stress (Gonmei, 2020). This emphasizes the importance of including the assessment of oxidative and antioxidant markers in the comprehensive diagnosis of babesiosis in dogs.

A study in eastern Slovakia demonstrated that *B. canis* in dogs was accompanied by significant clinical manifestations, including lethargy (91%), fever (59%), anorexia (59%), pigmenturia (47%), and jaundice (18%), with a mortality rate of 6% (Turna, 2022). The most characteristic hematological sign was thrombocytopenia (100%), confirming previous studies. Lymphopenia was found in 82% of cases and anemia in 68%, highlighting the systemic impact of the parasite on the circulatory system. A comparison of diagnostic methods showed the superiority of PCR over blood smear microscopy (PCR detected infection in 34 of 45 dogs, microscopy in 24), indicating the need for molecular diagnostics for accurate confirmation of cases (Turna, 2022).

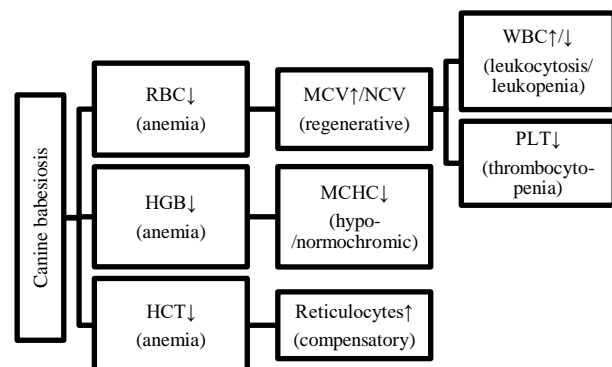
In Poland, analysis of 3,032 blood samples from dogs suspected of having babesiosis showed a prevalence of *B. canis* of 9.3% with two peaks of incidence per year (April and October) and increased susceptibility of purebred dogs (Pawelczyk, 2022; Pawelczyk, 2024). This highlights the regional and breed-specific characteristics of the disease, the need for seasonal epidemiological monitoring and timely diagnosis. A study of *B. canis* and *Dirofilaria repens* co-infections in Central Poland showed that *B. canis* mono-infection is accompanied by anemia and impaired liver and kidney function, while co-infection leads to less pronounced biochemical changes (Wężyk, 2023). Analysis of the immune response showed different profiles of Th1/Th2 and regulatory activity depending on the severity of the infection and the presence of co-infection. Thus, mild babesiosis was accompanied by

a predominance of Th2-response, severe – Th1 and regulatory mechanisms, and co-infection – a combined Th2 + regulatory response (Wężyk, 2023). These data emphasize the importance of assessing immune mechanisms and co-infections for predicting the clinical course of babesiosis and developing therapeutic strategies.

Thus, the results of these studies demonstrate that hematological parameters (Hb, Hct, RBC, MCV, MCHC) and biochemical markers (azotemia, electrolyte shifts, impaired glycemia and lipid profile) are key indicators of disease severity and prognostic factors in animals with babesiosis (Gonmei, 2020; Zaki, 2021; Galon, 2022; Kafrahi, 2024). In addition, molecular identification of the pathogen allows us not only to clarify the species affiliation of *Babesia*, but also to predict potential complications and the effectiveness of therapeutic measures.

A comprehensive analysis of all the presented studies allows us to identify key patterns of hematological and biochemical determinants of anemia in babesiosis (Fig. 3) (Gonmei, 2020; Zaki, 2021; Sajid, 2023; Kafrahi, 2024; Aziz, 2025):

1. Types of anemia: hemolytic or non-regenerative anemia prevails, sometimes with pancytopenia.
2. Hematological parameters: decrease in RBC, Hb, Hct; changes in MCV, MCH, MCHC within the framework of compensatory mechanisms; leukopenia or leukocytosis depending on the phase of infection.
3. Biochemical changes: increase in BUN, total bilirubin, AST, ALT, ALP; disturbances in electrolyte balance ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{P}^{5+}$ ), glucose and protein profile.
4. Pathogenetic mechanisms: direct damage to erythrocytes, immune-mediated mechanisms of hemolysis, oxidative stress, systemic intoxication.
5. Relationship between severity of clinical manifestations and laboratory changes: more severe hematological and biochemical disorders correlate with high parasitemia and severe clinical symptoms.



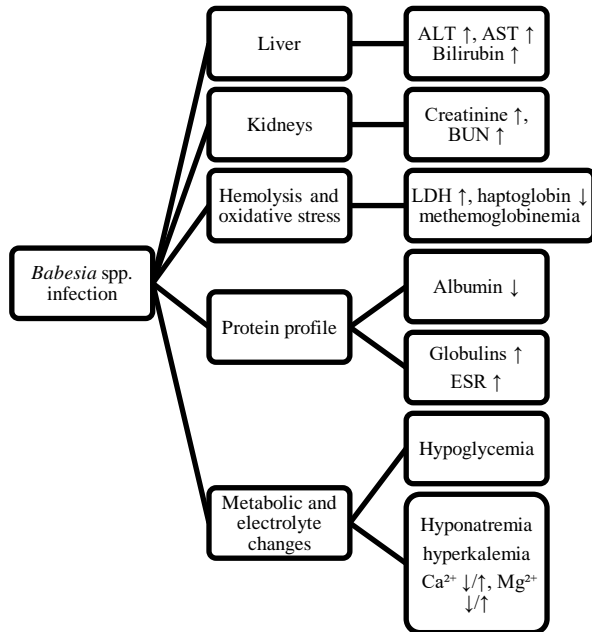
**Fig. 3.** Schematic representation of hematological determinants of anemia in canine babesiosis

Taken together, the results of international studies show that babesiosis in animals is accompanied by typical hematological abnormalities (anemia, thrombocytopenia, lymphopenia), changes in biochemical parameters (liver- and kidney-associated abnormalities, increased BUN), as well as impaired oxidative-antioxidant balance and variable immune response profiles. Molecular diagnostics by PCR are more reliable compared to microscopy of blood smears, especially in regions with low disease incidence.

### Biochemical determinants of babesiosis

Biochemical parameters in dogs and other animals infected with *Babesia* are key to assessing the severity of the disease, organ damage and oxidative stress (Nevidnyk-Pravda & Ushakova, 2025). They include parameters of liver and kidney function, markers of hemolysis and oxidative stress, protein profile, as well as metabolic and electrolyte abnormalities (Fig. 4). In babesiosis, elevated liver enzymes alanine (ALT) and aspartate aminotransferase (AST) are often observed, indicating hepatocellular damage (Table 1) (Gonmei, 2020; Goralska, 2024; Kafrahi, 2024). Total bilirubin may increase due to hemolysis of red blood cells and secondary jaundice, especially in cases of se-

vere infection (Turna, 2022; von Hohnhorst, 2025). Elevated creatinine and blood urea nitrogen (BUN) reflect renal dysfunction, which often accompanies hemolytic anemia and systemic intoxication in *B. canis* and *B. vogeli* (Gonmei, 2020; Wężyk, 2023; Kafrahi, 2024). A study in Mizoram (India) showed that dogs with confirmed *B. gibsoni* had elevated BUN, which correlated with the severity of clinical manifestations (Gonmei, 2020). Similarly, in Mashhad (Iran), dogs with *B. vogeli* were observed to have azotemia accompanied by hyperphosphatemia and hyperkalemia (Kafrahi, 2024).



**Fig. 4.** Main biochemical changes in animals with babesiosis

Hemolysis, characteristic of erythrocyte parasites, is reflected by an increase in lactate dehydrogenase (LDH) and a decrease in haptoglobin (Goralska, 2024; Zygner, 2023). Methemoglobinemia may occur as a consequence of oxidative stress in severe forms of babesiosis. The activity of markers of oxidative stress, in particular malondialdehyde (MDA), is increased, while antioxidant enzymes (superoxide dismutase (SOD), catalase) are reduced, which was recorded in the study of dogs in Mizoram (Gonmei, 2020; Teodorowski, 2021). These changes indicate that oxidative stress is an essential component of the pathogenesis of babesiosis and may be associated with the severity of anemia and impaired function of internal organs. Protein profile analysis in dogs with babesiosis shows a trend towards a decrease in albumin and an increase in globulins, which indicates the development of an acute phase reaction and an inflammatory process (Gonmei, 2020; Tóthová, 2020; Goralska, 2024). In wild Formosan black bears (*Ursus thibetanus formosanus*), *Babesia* spp. infection has been associated with increased globulins and elevated erythrocyte sedimentation rate (ESR), indicating a response to parasitic and ectoparasitic invasion (Tsai, 2024). In dogs infected with *B. canis* and *B. gibsoni*, decreased albumin has been associated with disease severity, including edema and impaired oncotic pressure (Tóthová, 2020). Metabolic changes in babesiosis include hypoglycemia, especially in severe cases and in young animals (Turna, 2022; Kafrahi, 2024). Electrolyte abnormalities include hyponatremia, hyperkalemia, and changes in calcium and magnesium, which may result from dehydration, hemolysis, and renal dysfunction (Kafrahi, 2024; Tsai, 2024). Analysis of bears showed that males and females had statistically significant differences in  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , and  $\text{K}^{+}$  concentrations, indicating gender-specific metabolic responses to infection (Tsai, 2024).

The biochemical determinants of babesiosis are complex and include changes in liver- and kidney-associated enzymes, markers of hemolysis and oxidative stress, protein profiles, and metabolic and electrolyte abnormalities. The observed changes correlate with the severity of infection, *Babesia* species, and housing conditions, and may reflect the degree of systemic inflammation and organ involvement.

The use of a comprehensive biochemical assessment, along with molecular diagnostics and hematological parameters, allows a more accurate assessment of the clinical status and prognosis of the disease in dogs and other animals (Gonmei, 2020; Goralska, 2024; Kafrahi, 2024; Tsai, 2024).

**Table 1**  
Biochemical markers and clinical significance

Marker	Change in babesiosis	Clinical significance	References
ALT, AST	↑	Hepatocellular injury	Gonmei, 2020; Goralska, 2024; Kafrahi, 2024
Bilirubin	↑	Hemolysis, jaundice	Turna, 2022; von Hohnhorst, 2025
Creatinine, BUN	↑	Renal dysfunction	Gonmei, 2020; Wężyk, 2023; Kafrahi, 2024
LDH	↑	Hemolysis	Zygner, 2023; Goralska, 2024
Haptoglobin	↓	Hemolysis	Zygner, 2023; Goralska, 2024
MDA	↑	Oxidative stress	Gonmei, 2020; Teodorowski, 2021
SOD, Catalase	↓	Reduced antioxidant defense	Gonmei, 2020; Teodorowski, 2021
Albumin	↓	Oncotic pressure disturbances, edema	Gonmei, 2020; Tóthová, 2020; Goralska, 2024
Globulins	↑	Acute phase response	Gonmei, 2020; Tóthová, 2020; Goralska, 2024; Tsai, 2024
Glucose	↓	Hypoglycemia, especially in severe/young cases	Turna, 2022; Kafrahi, 2024
$\text{Na}^{+}$	↓	Hyponatremia	Kafrahi, 2024; Tsai, 2024
$\text{K}^{+}$	↑	Hyperkalemia	Kafrahi, 2024; Tsai, 2024
$\text{Ca}^{2+}$ , $\text{Mg}^{2+}$	Variable	Metabolic response, gender differences	Tsai, 2024
CRP	↑	Acute phase protein, correlates with parasitemia	von Hohnhorst, 2025
SAA	↑	Acute phase response, early inflammation marker	Milanović, 2020
PON-1	↓	Antioxidant enzyme, decreased in chronic inflammation	Milanović, 2020

The development of an acute phase response (APR) in *B. canis* is a key indicator of the activation of systemic inflammation, even in cases without clinical symptoms. Asymptomatic dogs infected with *B. canis* have increased concentrations of serum amyloid A (SAA) and decreased activity of the antioxidant enzyme paraoxonase-1 (PON-1), suggesting the presence of chronic low-grade inflammation (Milanović, 2020). Increased total protein and changes in the  $\alpha$ -lipoprotein profile confirm the presence of APR even in the absence of clinical signs.

In acute *B. canis* infection in dogs, the most common abnormalities are thrombocytopenia (85–100%), anemia (70–80%), lymphopenia (80%), and hyperbilirubinemia (up to 74%) (Turna, 2022; von Hohnhorst, 2025). Associated biochemical abnormalities include elevated C-reactive protein (CRP), which is found in over 80% of cases and is significantly correlated with parasitemia ( $\rho = 0.444$ ) (von Hohnhorst, 2025).

High titers of antibodies against *B. canis* are associated with lower parasitemia and less severe clinical and hematological abnormalities (von Hohnhorst, 2025). This supports the protective role of humoral immunity in controlling *Babesia* infection and explains the milder course of the disease in dogs that have had previous exposure to the parasite.

Dogs without previous exposure to *B. canis* (seronegative but PCR-positive) demonstrate higher CRP levels, more severe anemia and thrombocytopenia, and a higher hematological score (HES) compared to immunologically prepared animals (von Hohnhorst, 2025). This indicates the key role of adaptive immunity in shaping the clinical picture and prognosis.

Acute phase proteins (SAA, CRP), antioxidant enzymes (PON-1), and antibody titers against *Babesia canis* are reliable biomarkers of the course of infection. Their comprehensive assessment allows us:

- to differentiate asymptomatic and clinical forms of the disease;
- to predict the severity of the course depending on the immune status of the animal;
- to clarify the role of humoral immunity in the control of parasitemia.

These data highlight that even in the absence of symptoms, *B. canis* infection is accompanied by a systemic inflammatory response, which may be an early predictor of the transition to the clinical form.

### Problems and prospects of babesiosis

Despite significant progress in the development of diagnostic methods, a number of problems still remain.

Blood smear microscopy, which is widely used in veterinary practice, is characterized by low sensitivity, especially at low levels of parasitemia and in cases of chronic or subclinical infection (Kafrahi, 2024). In the study by Kafrahi et al. (2024) in Iran, the prevalence of babesiosis according to PCR was 15.3%, while microscopy detected only 2% of infected animals, which confirms the limited diagnostic value of traditional methods. Serological methods allow to detect previous contact with *Babesia* spp., but do not allow to determine the activity of the infectious process. At the same time, positive antibody titers can persist after elimination of the parasite, which complicates the interpretation of the results (von Hohnhorst, 2025). Molecular methods (PCR, qPCR, LAMP) provide high sensitivity and specificity, but they require specialized equipment, high cost of reagents and are not always available in routine veterinary practice (Kuo, 2020).

Monitoring the severity of the course is mainly based on the assessment of clinical and hematological indicators, but there are no standardized scoring systems that could be used in daily practice. The use of hematological scores (e.g. HES in the study of von Hohnhorst et al., 2025) shows potential, but requires unification and validation (von Hohnhorst, 2025).

Anemia is one of the most frequent and important manifestations of babesiosis (Zygner, 2023). However, its assessment in veterinary practice is often limited to determining the level of hematocrit (Hct) or hemoglobin concentration. A number of studies indicate the need to expand this approach:

- determination of the type of anemia (regenerative or non-regenerative) (Kafrahi, 2024);
- analysis of morphological changes in erythrocytes (Dubova, 2005b);
- assessment of the role of proinflammatory cytokines in the pathogenesis of anemia (Zygner, 2023);
- combination of hematological and biochemical markers to determine prognosis (e.g., CRP, ferritin, iron, oxidative stress indicators) (Teodorowski, 2021; Zaki, 2021).

Development of single standardized protocols for assessing the severity of anemia will increase the accuracy of diagnosis, unify results between studies and optimize therapeutic decisions.

Recent work demonstrates the potential of new diagnostic markers:

- acute phase proteins (SAA, CRP), which reflect the degree of systemic inflammation even in asymptomatic animals (Milanović, 2020);
- antioxidant and oxidative biomarkers, including PON-1, markers of lipid peroxidation, which correlate with the severity of the course (Teodorowski, 2021; Zaki, 2021);
- immunological markers, in particular the expression of TNF- $\alpha$  and IFN- $\gamma$  genes, which are increased in dogs infected with *B. vogeli* and can be used to predict the course of the disease (Zaki, 2021).

The development of portable molecular platforms for field conditions (e.g., using TaqMan-PCR or LAMP technologies) (Kuo, 2020) is promising. They can become the basis for rapid and more accurate diagnostics, especially in countries with a high prevalence of babesiosis. The presence of co-infections (e.g., *Ehrlichia canis* together with *B. vogeli* in Egypt (Zaki, 2021)) or latent forms of babesiosis creates additional challenges for treatment. Promising directions are:

– development of individualized therapy regimens that take into account the level of parasitemia, immune status and concomitant infections;

- study of the synergy of antiparasitic drugs with anti-inflammatory and antioxidant agents (Strobl, 2020);
- study the possibilities of immunomodulatory therapy based on cytokines or biological agents to reduce the systemic inflammatory response (Djokic, 2021; Zygner, 2023).

Current problems in the study of canine babesiosis include low sensitivity of routine diagnostic methods, lack of standardized protocols for assessing the severity of anemia and insufficient availability of molecular diagnostics in practical veterinary medicine. Further research should be aimed at integrating new biomarkers (acute phase, immunological, oxidative), implementing available molecular technologies and optimizing combination therapy taking into account co-infections.

An important direction of modern research is the comparison of the prevalence of babesiosis and related piroplasmoses in different animal species and regions, which allows a better assessment of the risks for dogs and the development of universal approaches to monitoring.

A study in Erbil Province (Iraq) showed that *Theileria equi* and *Babesia caballi* are significant pathogens of racehorses with a prevalence of 22.4% and 8.2%, respectively (Aziz, 2025). Affected horses had microcytic anemia, elevated liver enzymes (AST, ALT, ALP) and bilirubin levels, as well as hypoproteinemia and hypoglycemia. These results confirm that the mechanisms of pathogenesis of piroplasmosis in different species (horses and dogs) share common features – hemolytic anemia, hepatobiliary lesions and metabolic changes. In Taiwan, a study of the Formosan black bear (*Ursus thibetanus formosanus*) population showed a high prevalence of *Hepatozoon ursi* (61.9%) and *Babesia* spp. (38.1%) (Tsai, 2024). Pathogens were associated with changes in globulin fractions and elevated ESR, and ectoparasitic ticks were infected with both pathogens at high frequencies (53–65%). This suggests that wild animals are reservoir hosts and maintain the circulation of babesiosis in natural biocenoses.

In a study in Southern Thailand, the blood of parasitically infected dogs showed significant hematological changes: a decrease in the number of erythrocytes, hemoglobin and hematocrit, as well as thrombocytopenia. The authors noted that infections with *Babesia* spp. and other blood parasites correlated with anemia and coagulation disorders, emphasizing the clinical significance of monitoring the hematological profile for the diagnosis and management of the disease (Thongsahuan, 2020).

A retrospective analysis of 3,032 dog samples in Southern Poland (2018–2022) showed that 9.3% of cases were positive for *B. canis* (Pawelczyk, 2024). A pronounced seasonality (peaks in April and October) and an increased susceptibility in purebred dogs were found. An additional study of the range of *Dermacentor reticulatus* (2016–2018) confirmed that the expansion of the tick distribution area was accompanied by an increase in babesiosis cases in dogs, with the incidence reaching 250 cases per 1000 dogs in Eastern Poland with a mortality rate of 3.65% (Dwużnik-Szarek, 2021). This indicates a direct spatiotemporal correlation between the dynamics of the tick range and the risk of babesiosis.

Analysis of international data confirms that:

- 1) cross-species parallels (dogs, horses, wild animals) demonstrate universal pathogenetic mechanisms, mainly through hemolytic anemia, hepatic and metabolic lesions;
- 2) the reservoir role of wildlife is key in maintaining the circulation of *Babesia* spp. in natural conditions;
- 3) the geographical features of Central and Eastern Europe (in particular, Poland) are of direct importance for Ukraine due to the similarity of climate and areas of vector ticks, which allows us to predict similar trends in the spread of babesiosis in domestic conditions.

### Conclusions

Canine babesiosis remains one of the most significant tick-borne diseases affecting dogs worldwide, with complex pathophysiology,

variable clinical manifestations, and diverse epidemiological patterns. Despite considerable research, the full impact of *Babesia* infections on canine health is often underestimated, particularly in relation to subclinical infections, hematological alterations, and systemic complications. Historically, understanding of babesiosis has evolved from simple recognition of acute hemolytic episodes to complex models encompassing host-pathogen interactions, immune responses, vector ecology, and regional epidemiology. Recent advances in molecular diagnostics, epidemiological monitoring, and clinical management have expanded our knowledge, yet many aspects remain incompletely understood.

The reviewed literature demonstrates that *Babesia* infections can lead to a wide spectrum of clinical manifestations, ranging from asymptomatic parasitemia to severe, life-threatening disease. Hematological changes, including anemia, thrombocytopenia, and leukocyte alterations, are consistently reported, as are biochemical disturbances affecting liver and kidney function, protein metabolism, and oxidative stress markers. These alterations reflect a multifactorial pathophysiology involving direct parasitic destruction of erythrocytes, immune-mediated mechanisms, systemic inflammatory responses, and oxidative damage. The integration of molecular diagnostics with clinical and laboratory findings has improved the accuracy of *Babesia* species identification, enabling more precise epidemiological mapping and targeted therapeutic interventions.

The epidemiological review underscores the significance of vector distribution, particularly *Dermacentor reticulatus* and other ixodid ticks, in shaping regional disease prevalence. Human-mediated factors, such as dog movement and changes in land use, as well as climate-driven expansion of tick habitats, contribute to the emergence of new foci and increased disease risk in previously non-endemic areas. Additionally, wild reservoir hosts, including jackals and foxes, play a crucial role in maintaining *Babesia* circulation in natural ecosystems, complicating control measures in domestic dog populations.

Therapeutic management remains a key challenge, as antiprotozoal treatments are often species-specific and may be insufficient in severe cases without supportive care addressing anemia, organ dysfunction, and systemic inflammation. Studies indicate that early recognition, accurate diagnosis, and prompt initiation of therapy significantly improve outcomes, but chronic and relapsing infections highlight the need for long-term monitoring and comprehensive preventive strategies, including tick control and vaccination research.

Despite these advances, several obstacles impede progress in fully understanding and controlling canine babesiosis. These include the complexity of host-pathogen-vector interactions, limitations in routine laboratory diagnostics for subclinical or mixed infections, regional variations in clinical presentation, and gaps in veterinary education regarding emerging *Babesia* species. Additionally, insufficient epidemiological surveillance and inconsistent reporting hinder the ability to implement standardized preventive measures and treatment protocols across different regions.

Potential solutions to these challenges include: (1) expanded epidemiological research to clarify regional prevalence, tick ecology, and reservoir host dynamics; (2) development and implementation of standardized diagnostic protocols combining microscopy, serology, and molecular methods; (3) integrated vector control strategies, including habitat management and acaricide application; (4) improved education and training of veterinary professionals in recognizing and managing babesiosis; and (5) multidisciplinary collaboration among parasitologists, clinicians, immunologists, and epidemiologists to enhance understanding of disease mechanisms and treatment efficacy.

Further investigation is needed to better characterize subclinical infections, host immune responses, and long-term sequelae of canine babesiosis. Molecular studies may expand the known diversity of *Babesia* species and their pathogenic potential, while prospective clinical studies can provide more robust data on therapeutic outcomes and complications. Development of predictive models integrating host factors, parasite load, and vector ecology may support early detection and preventive strategies. Strengthening veterinary education and promoting international collaboration will be crucial for advancing un-

derstanding, improving diagnosis and treatment, and reducing morbidity and mortality associated with canine babesiosis.

A comprehensive analysis of literature sources and our own observations shows that canine babesiosis is a complex multifactorial disease, in the pathogenesis of which the leading role is played by anemic syndrome, hepatorenal disorders and metabolic changes.

The main pathogenetic mechanism is massive intravascular and intracellular hemolysis of erythrocytes under the influence of *Babesia canis*.

A decrease in the number of erythrocytes, hematocrit (PCV) and hemoglobin is observed, which forms the clinical picture of regenerative or aregenerative anemia.

Affected animals often have leukocytosis, lymphocytosis and an increase in the percentage of basophils, which indicates an immune response to the infection. Similar mechanisms have been noted in horses infected with *Theileria equi* and *Babesia caballi* (microcytic anemia, changes in WBC). Typical are increased liver enzymes (AST, ALT, ALP), hyperbilirubinemia, indicating hepatobiliary lesions. Hypoproteinemia and hypoalbuminemia develop, decreased calcium and glucose, which causes energy and metabolic disorders. Similar changes were noted in horses in Iraq and in wild Formosan black bears in Taiwan, where parasitic infection was associated with changes in protein fractions and electrolyte balance.

In Ukraine, cases of babesiosis have been registered in Zhytomyr and Dnipropetrovsk regions, which indicates active circulation of the pathogen and the risk of spread to other regions. Data from Poland confirm that the spread of *Dermacentor reticulatus* ticks directly correlates with the frequency of babesiosis in dogs, with pronounced seasonality and high mortality. This allows us to predict similar processes in Ukraine given the similarity of climatic conditions and the range of ticks. Wild animals (e.g., Formosan black bears) act as a natural reservoir of infection, supporting the circulation of *Babesia* spp. in biocenoses.

Since anemia in babesiosis is of hemolytic origin, the therapeutic strategy should include not only the use of specific antiprotozoal drugs (imidacloprid, azidine, diminazene), but also measures to maintain hematological and biochemical parameters.

The following are important:

- infusion therapy to correct hypovolemia and intoxication;
- hepatoprotectors to reduce liver damage;
- blood transfusion for severe anemia;
- restoration of protein and energy balance through nutritional support.

Thus, treatment should be comprehensive and aimed not only at eliminating the pathogen, but also at correcting the consequences of its pathogenic action.

The review combines the results of international studies (Iraq, Taiwan, Poland) with regional Ukrainian data, creating a holistic picture of the spread and pathogenesis of babesiosis. Generalization of hematological and biochemical markers of anemia is of direct importance for practical diagnostics, monitoring and prognosis of the course of the disease in dogs. Taking into account interspecies parallels (dogs – horses – wild animals) opens up prospects for universal models of pathogenesis and improvement of therapeutic protocols. For veterinary practice in Ukraine, this is especially important given the risk of further spread of babesiosis due to the expansion of the areas of vector ticks.

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