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Dirofilaria immitis: Global Status and Recent Advances

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ABSTRACT

Dirofilaria immitis is a mosquito-borne zoonotic nematode causing serious disease in dogs and transmissible to humans. Its epidemiology varies with vector biology, climate, and temperature. Recent years have seen rising infection rates, driven by increased pet ownership, easier dog travel, heightened mosquito activity in holiday resorts, and changes in wildlife habitats. Further accelerating its spread are insufficient awareness among pet owners, veterinarians failing overlooked clinical signs, inadequate diagnostic testing, and the dissemination of outbreaks from animal shelters. This review consolidates the latest global data on the parasite's clinical characteristics, diagnosis, treatment, and epidemiology. Despite scientific and technological advances, mosquito-borne Dirofilaria immitis remains widespread, often undiagnosed, and increasingly prevalent in subclinical forms, underscoring the urgent need for improved prevention and control strategies.

Keywords: *Dirofilaria immitis, mosquito, global status, global climate change, recent advances.*

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Materials and Methods

This systematic review comprehensively assesses current *literature* on *Dirofilaria immitis* infection, detailing its biology, life cycle, pathogenesis, diagnostic methods, treatment protocols, epidemiological distribution, and zoonotic importance. A systematic search was performed across PubMed, ScienceDirect, Google Scholar, Scopus, and Web of Science for scientific articles, reviews, and guidelines published in English and Turkish between 2000 and 2025. Keywords included "*Dirofilaria immitis*," "heartworm disease," "canine filariasis," "Wolbachia," "vector-borne nematodes," and their synonyms. Inclusion criteria were peer-reviewed, full-text sources presenting original data on D. immitis's etiology, epidemiology, diagnosis, treatment, or zoonotic risk. Epidemiological data, including comparative prevalence rates for various continents and countries, were evaluated, with a specific focus on current prevalence in Turkey. Information was classified, structured into sections, and appropriately cited. The review aims to contribute to clinical veterinary medicine and raise awareness of *D. immitis.*

Introduction

Dirofilaria immitis, a zoonotic nematode transmitted by mosquitoes, causes disease in dogs, cats, and humans. While adult worms primarily reside in the pulmonary artery of dogs, they can also manifest in the skin, bronchioles, eyes, and brain, causing localized pathologies. Common canine symptoms include coughing, early fatigue, dermatitis, dyspnea, ascites, and right heart failure. Its larval stage, microfilariae, circulates in the blood, triggering immune responses. In humans, microfilariae can

cause disease, but adult worms typically do not develop or settle in the heart (Eroğlu, F., 2017).

Mosquitoes are critical for *D. immitis* transmission, with air temperature and climate zones significantly influencing the infection's epidemiology. Beyond these geographical factors, mosquito species, population density, public and dog owner awareness, and veterinary knowledge also impact prevalence. While various drugs and treatment methods exist, preventive medicine remains the most important tool against this parasite.

Recent years have seen increased awareness and diversified diagnostic methods leading to a rise in *D. immitis* diagnoses, including in non-endemic areas, which raises new epidemiological questions. The array of diagnostic methods and potential ambiguities in result interpretation can complicate clinical management for veterinarians. Moreover, selecting treatment protocols is often influenced by the patient's clinical condition, diagnostic method, and owner's financial capacity.

1.*Dirofilaria immitis* biology and life cycle

Dirofilaria immitis, a nematode of the Onchocercidae family, has a collagenous body covered by a protective cuticle, which shields it from the host's immune system. These parasites possess longitudinal muscles. Males are spiral-shaped with cuticle bulges, while females are flat. Sexually dimorphic, males have testes and a seminal vesicle, whereas females possess ovaries and oviducts. These long, cylindrical adults measure 15-18 cm (males) and 18-30 cm (females). Adult females produce 307-322 µm long, 6-7 µm wide microfilariae, characterized by sharp posterior and blunt anterior ends. The parasite's life stages are designated L1-L5, followed by the adult stage, though some researchers consider L5 an early adult stage (Animal Diversity Web.2025; Mehlhorn, H. (2016)).

Dogs are the final hosts for *D. immitis* ; reproduction and proper development only occur in their pulmonary artery and right heart (Mehlhorn, H. (2016)). While *D. immitis* can be found in ectopic locations such as the eye, skin, or left heart, microfilariae produced there either fail to enter circulation or cannot adequately reproduce due to immune system pressure. Numerous other mammals, including foxes, coyotes, cats, wolves, raccoons, horses, and humans, can be infected, but these are typically non-progressive infections. Adult worms rarely form or, if they do, fail to produce microfilariae. However, the presence of larvae can still lead to pathogenic conditions (Animal Diversity Web.2025).

Mosquitoes (Aedes, Culex, Anopheles) serve as intermediate hosts, ingesting L1 microfilariae during blood meals from infected final hosts. Within the mosquito's Malpighian tubules, L1 develops into L2, then progresses to the infective L3 stage in the hemocoel, a process taking 2-3 weeks. The L3 larvae are then transmitted to a new host when the infected mosquito bites. In the new host, L3 molts to L4 within 2 weeks. L4 larvae migrate to subcutaneous tissues, molt to L5, and then traverse vein walls to reach the pulmonary arterioles and right heart (Liu SK.1966). There, they mature into adults, residing in the right ventricle or pulmonary artery. Maturation to adult and subsequent mating, leading to microfilariae production, takes approximately 2 months (Mehlhorn, H. (2016)). Adult parasites can live up to 7 years, while microfilariae persist in the bloodstream for up to 2 years (Brusca, R.2003). While L4 larvae occasionally migrate to ectopic sites like the eye, brain, vena hepatica, or subcutaneous tissues, adult development and reproduction are restricted to the pulmonary artery and right heart (Animal Diversity Web.2025).

Table 1. Development Stages of Dirofilaria immitis

Stage	Description
L1	Microfilariae, the first larval stage that enters the bloodstream
L2	The second larval stage developing in the mosquito
L3	Infectious larval stage (mosquito-to-host transmission)
L4	Larval stage developing in subcutaneous tissues
L5	Maturation stage (early adult)
Mature	Form found in the pulmonary arteries and right heart

Female nematodes attract males via pheromones. During copulation, the male wraps around the female, using spicules for stability and its gubernaculum to locate the cloaca and anus (Brusca, R.2003). Microfilariae circulate in the blood, peaking around 20:00 and reaching their lowest levels around 08:00. This periodicity facilitates uptake by nocturnal mosquito intermediate hosts (Aranda, C. et al. 1998).

Wolbachia pipientis is an intracellular, gram-negative bacterium that forms a crucial symbiotic mutualistic relationship with the filarial parasite *Dirofilaria immitis,* essential for its development and reproduction. These bacteria are found in the

hypodermal cells of the lateral cord throughout all parasite developmental stages, as well as in the ovary, eggs, and developing embryos of female parasites. Their absence in male reproductive organs suggests transmission primarily occurs via egg cytoplasm. Bacterial numbers remain constant during the microfilaria and L2-L3 stages within the insect host, but significantly increase after transfer to the mammalian host. In this symbiosis, *D. immitis* provides suitable conditions for Wolbachia's survival and reproduction, while Wolbachia offers metabolic support, enabling the parasite to evade host immunity and regulate its reproductive activities (Mark J. Taylor et al. 2005). This indispensable role is further evidenced by the observation that antibiotic-mediated elimination of Wolbachia impairs *D. immitis* reproduction and development.

2. Epidemiology of Dirofilaria immitis and Current Situation in the World and Turkey

Dirofilaria immitis infection is prevalent in tropical, subtropical, and temperate climates. Its distribution correlates strongly with the presence of mosquito vectors and dense canine populations (Anvari et al., 2017). Key vector genera include *Aedes* (optimal 25-30°C), *Culex* (optimal 20-25°C), and *Anopheles* (optimal 25-28°C). Larval development, however, ceases below 14°C (Fortin et al., 1981). Therefore, for *D. immitis* to establish, regions must sustain optimal temperatures for at least two weeks and maintain a high density of dogs, its final hosts (Anvari et al., 2017). Such conditions are found in areas like the Mediterranean basin, parts of the American continent, Southern Europe, North and Central Africa, Australia, and certain parts of Asia.

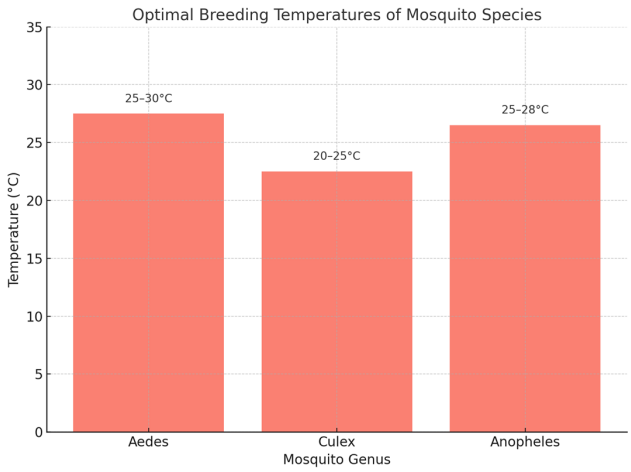

Figure 1. Optimal temperature ranges for mosquito species.

In a study conducted in 2020, the most up-to-date data on the continental basis calculated the following rates for *Dirofilaria immitis* infection in dogs: Australia 22.68% (95% CI: 6.30-45.37), Asia 12.07% (95% CI: 9.12-15.37), America 11.60% (95% CI: 10.47-12.77), Europe 10.45% (95% CI: 7.51-13.82) Africa 7.57% (95% CI: 3.09-13.80) (Anvari D. et al. 2020; J. Guerrero et al. 2006; John W. McCall et al. 2008). *D. repens* infection is observed more than *D. immitis* infection in Europe (Genchi, C. 2020). The breed, age, gender and weight of the animal are not important in the prevalence of the parasite's transmission and development, but since the parasite is transmitted by intermediate hosts, factors such as the time spent outdoors by the intermediate host mosquito to bite, sparse hair or bare areas, and the large size of the animal will increase mosquito contact and therefore are thought to increase the prevalence.

Climate zones have been changing in recent years due to climate change and global warming. For this reason, the spread and development areas of mosquitoes are increasing with the increase in regional normal temperatures. In a study conducted in Russia, it was observed that the climate zone where suitable temperatures for mosquitoes occur has increased from 43 degrees longitude to 58 degrees longitude in the last 20-25 years and mosquito interactions have increased (Kondrashin, A. V.2022). In another study, it is predicted that the spread of *Culex pipiens* in the Iberian Peninsula is increasing and will increase by approximately 50% in the near future, and therefore, *Dirofilaria immitis* infections will increase (Rodríguez-Escolar et al. 2023). Turkey is located in the Mediterranean climate zone, which is one of the climate zones suitable for the development and spread of this parasite. Studies show that awareness and consciousness against this parasite is increasing among veterinarians and animal owners in our country. In a study conducted in Aydın province in 2020, it was seen that the prevalence of *Dirofilaria immitis* in owned dogs was 10% (Sarali, H. Et al. 2020). In a study conducted in Kayseri in 2007, the positivity rate was measured as 9.7% (A. Yıldırım et al. 2007). In a study conducted in Burdur, it was determined that the latent infection rate in street dogs was 35.5%. (Adanır, R. et al. 2013) In a study conducted in Hatay in 2009, the positivity rate was measured as 26%. In a study conducted in 2008 with ELISA test on street dogs and owned dogs, the

seropositivity rate was measured as 18.3% in Kocaeli, 14.8% in Ankara, 12.3% in Sakarya and 10.5% in Mersin (Simsek S et al. 2008). In a study conducted on street dogs from Istanbul and Izmir in 2002 and 2003, the positivity rate was found as 1.52% in Istanbul and 0% in Izmir (Öncel, T., Vural, G. 2005). In light of these studies, it is thought that a more extensive and up-to-date study on owned dogs is necessary.

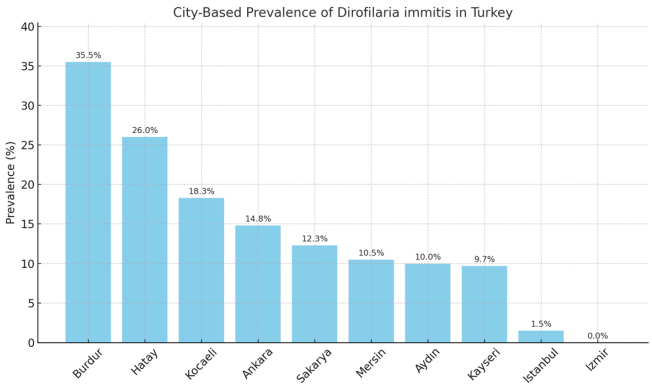

Figure 2. Prevalence rates in various provinces of Turkey by year.

3. Pathogenesis

This parasite causes a number of pathological effects on the final host, both in its larval form and in its adult form, and with the Wolbachia bacteria it contains (Mark J. Taylor et al. 2005). If we consider them in order, the L3, L4 and L5 forms found in the final host cause reactions in the body, although not as much as the adult form. The most common of these are eosinophilia, glomerulonephritis and pneumonia. Some animals may also show hypersensitivity reactions to microfilariae found in the blood. In addition, it has been observed that larvae pass to different organs and tissues with perverse parasitism during larval migration. Systemic arteries, the anterior chamber of the eye, and the urinary bladder are among these reported (Perles, L. et al. 2024) (Liu SK. 1966). It has been observed that dogs with microfilariae in the bloodstream have higher levels of interleukin (IL)-4, IL-10 and inducible nitric oxide synthase (iNOS) mRNA compared to those with latent infection; this suggests that the presence of microfilariae is associated with immune tolerance to infection (R. Morchón et al. 2007).

Adult forms can cause very different pathological reactions depending on their location and the response of the host's immune system. The final target of adult parasites in the final host is the pulmonary arteries. Apart from this, they can also be seen in the lung parenchyma and the right heart. When they are present here, they cause pulmonary hypertension, and if their numbers are high, they cause congestive heart failure over time unless treated. Their presence and movement cause damage and thickening of the vascular endothelium. Another important pathological effect is Caval syndrome. In this disorder, when the parasites are found in large numbers in the vena cava and right atrium, they block blood flow and cause sudden onset of acute hemolysis and hemoglobinuria. Death occurs if not treated in a short time (R.B. Atwell, I.B.J et al.1988). Usually, more parasites accumulate in the right caudal lobe artery, which is larger and more accessible than in the left lobe. The initial lesions are limited to the small peripheral branches where the parasite first settles. As the parasite grows, lesions occur in more proximal segments. Thickening and narrowing of the vessels in the peripheral branches of the pulmonary arteries cause obstruction of flow and pulmonary hypertension. Thrombosis and thromboembolism may also be seen.

The most common responses of the host's immune system to these parasites are eosinophilia and hypergammaglobulinemia. Immune system components formed against the parasite and immune complexes formed by the antigens of the parasite accumulate in the kidneys and may lead to glomerulonephritis. In addition, due to right heart failure, blood pooling in the liver and subsequent liver damage may occur. It has also been observed that the body creates immune responses against the Wolbachia bacteria carried by the parasite.

Symptoms observed in the host include difficulty breathing, edema in the body in general or in the limbs, exercise intolerance, pododermatitis, and the presence of parasites in the eye as a result of perverse parasitism (Weiner, D. J. et al. 1981).

4. Diagnostic methods

Various methods can be used in the diagnosis of *Dirofilaria immitis* in the final host. The aim of the diagnosis is to search for microfilariae and adult parasites. For this reason, while the blood of the final host is examined microscopically when searching for microfilariae, different methods can be used to search for adult parasites. These methods include searching for antigens of the parasite in the blood of the final host with the ELISA method and the PCR method, observing the adult worm in the heart with echocardiography, evaluating the condition of the heart with radiography and electrocardiography, and

cytological and histopathological examination of tissue and fluid samples in cases where it can be seen in different tissues as a result of aberrant parasitism.

The aim in searching for microfilariae is to detect live microfilariae circulating in the blood. For this purpose, blood taken from the final host, preferably from the vena jugularis or vena cephalica veins, can be examined. Taking the sample at night, when microfilariae are seen in the highest numbers in circulation, preferably between 18:00 and 06:00, increases the chance of seeing the parasite (Mathison, B. A.2019; Aranda, C. Et al.1998). This blood, which will be used to search for microfilariae, can be used for different diagnostic methods. These are the thick drop method, the Filtration method, the Modified Knott method and the blood smear and microfilariae search methods.

The thick drop method is the simplest and cheapest method, but it can give false negative results in cases of low parasitemia. In this method, a drop of blood taken from the final host is dropped onto a slide, approximately 50 µl, covered with a coverslip and examined under a microscope at 100x, 200x and 400x magnifications. The microfilariae are sought to be mobile and to make a fluttering movement in place. Seeing even a single one means a positive result and is the fastest and cheapest diagnostic method in normal-high parasitemia cases (Smith, R.C. et al.2024). The number of microfilariae per milliliter is calculated by multiplying the counted parasite amount by 50. In this method, in the examined blood sample, *Acantocheilonema* microfilariae make progressive movements forward in the direction of the head, while *Dirofilaria* microfilariae make fluttering movements in place (Janice L. et al.2013).

In the blood smear method, 4 µl of blood is placed on the end of the slide and a smear is prepared at a 45-degree angle and dried on the slide, the dried slide is fixed with methanol and preferably stained with a Romanowski stain (Giemsa, Wright Giemsa, etc.) and examined under a microscope. In this method, due to the size and weight of the parasites, parasites are searched for at the point where the smear ends, called the “feathered edge” of the blood smear, where the cells are sparse. It is expected that the detected parasites are immobile and their body structures are stained. Again, similar to the thick drop method, false negative results may be observed in cases of low parasitemia (Smith, R.C. et al.2024).

In the filtration method, approximately 1 ml of blood taken from the host is hemolyzed with lysine or formalin and this mixture is passed through some commercial filter papers and the remaining liquid is stained with a Romanowski type stain under a microscope. The parasites are expected to be monitored in a motionless state. It is a highly sensitive test, but due to the availability of easier and faster diagnostic tests, commercial kits are no longer available.

In the modified Knott test, 1 ml of blood taken from the host is placed in a tube, 9 ml of 2% formalin is added and inverted several times. Then, it is centrifuged at 1409g for 5 minutes. The supernatant that has accumulated on the mixture is poured without shaking and 1 drop of methylene blue is dropped into the remaining sediment and left for 2 minutes. Then, this stained sediment is completely taken and placed on a slide, covered with a coverslip and examined under a microscope at low magnification (Knott J.1939; Smith, R.C. et al.2024). This method is easy and cheap, and has high sensitivity, and also allows morphological examination and differentiation from other similar blood parasites that may be found in blood, such as *Acantocheilonema* and *Dirofilaria repens.* The cephalic cavity of *Dirofilaria repens* is short and a distinct pair of nuclei are seen at the head end. The cephalic cavity of the smaller *Dirofilaria immitis* microfilaria is longer and does not contain distinct nuclei separated from the somatic nuclear column at the anterior end. This feature of the head cavity is a criterion that can be routinely used to easily distinguish these two larvae on stained blood smears. In addition, the diagnosis can be made by comparing the lengths of these three most frequently encountered parasites. The length and width of microfilariae were reported as 301.77 ± 6.29 µm and 6.30 ± 0.26 µm for *Dirofilaria immitis*, 369.44 ± 10.76 µm and 8.87 ± 0.58 µm for *Dirofilaria repens*, and 264.83 ± 5.47 µm and 4.63 ± 0.52 µm for *Acantocheilonema reconditum*, respectively (Janice L. et al. 2013; Magnis, J. et al. 2013).

The investigation of the presence of adult parasites may vary depending on the current condition of the sick dog, the symptoms it gives, and the anamnesis given by the owner. After microfilariae are seen in the blood of an asymptomatic animal, it can be monitored with various methods such as cardiac echocardiography, electrocardiography, radiography

in order to search for adult parasites, serological and molecular tests can be performed on the blood, and parasites can be seen incidentally in the cytological preparation taken from the lesioned area of a dog with wounds on its skin and feet. The most frequently applied diagnostic method clinically is the detection of the antigen of the adult parasite in suspicious cases or general health screenings and then direct treatment or observation of the adult parasite in the pulmonary artery of the heart with echocardiography.

Other laboratory tests used in the search for parasites are ELISA and PCR tests.

The ELISA (Enzyme-Linked Immunosorbent Assay) method is based on the search for the antigen of the female adult nematode in a blood sample. For this reason, ELISA tests produced by various different brands can be used over the years. These tests offer the opportunity to diagnose the infection in earlier or microfilaria-negative periods, regardless of the presence of microfilaria. ELISA tests can be applied with serum or plasma samples and detect uterine antigens belonging to adult female *Dirofilaria immitis*. These antigens usually become detectable in the blood 6-8 months after infection. If only male adult parasites are present, if the antigen level in the sample blood is low, if the parasites are dead, if immune complexes have formed against the antigens, these may lead to false positive or negative results, but they are still very useful and clinically useful tests. False negative results due to the immune complexes formed can be eliminated with the immune complex dissociation (ICD) technique. (Barrantes Murillo et al.2024). For this reason, it is recommended to hold the blood sample at 105 degrees for 10 minutes and then test it. In a study conducted in the USA using this method, the prevalence of *Dirofilaria immitis* calculated from different states was 3.8% before the ICD technique was applied, but it increased to 7.3% when the samples were retested after the ICD technique was applied. In another study conducted in Italy on shelter dogs, the *Dirofilaria immitis* antigen positivity rate in blood samples examined without the ICD technique was 56.5%, while the positivity rate increased to 79.6% after the ICD technique was applied. In this study, it was stated that the majority of the blood samples that turned positive from negative were previously seen as *Dirofilaria immitis* antigen negative and *Dirofilaria repens* antigen positive (Panarese, R. Et al.2020). Although the ICD technique is not very useful in clinical practice, it is recommended that laboratories should apply it for samples with high suspicion. (Barrantes Murillo et al.2024)

The PCR (Polymerase Chain Reaction) method is based on the principle of searching for *Dirofilaria immitis* DNA in blood. The DNA of the gene in the examined blood sample is amplified and multiplied. The most commonly targeted gene regions include ITS2 (Internal Transcribed Spacer 2), 12S rRNA and COI (Cytochrome Oxidase I) genes. These regions are suitable for both recognizing the parasite and differentiating it from similar species such as *Dirofilaria repens* (Smith, R.C. et al.2024). In addition, thanks to phylogenetic analyses, genetic variations and evolutionary relationships of *Dirofilaria immitis* isolated from different geographies can be investigated. PCR has higher sensitivity and specificity than the other mentioned tests, and it also has a high value in species discrimination. However, it is expensive, the test results take longer, and in clinical practice, it is a method used if suspicion of infection persists when negative results are seen in ELISA tests and microscopic tests (Smith, R.C. et al.2024). Commercial tests are sold and also applied in laboratories.

When all these laboratory tests are compared, PCR and Modified Knott methods give the best results even at low microfilar concentrations in the unit blood, and results are obtained even at a blood concentration of 25 microfilar/ml. At concentrations such as 50 microfilar/ml blood, parasite detection can be done with other methods such as blood smear. Although PCR has a high accuracy rate, its area of use is narrower due to the high test costs, long test duration, and the need for experts in the field in the application.

Complete blood count data in blood tests are not pathognomonic, but can give an idea. Eosinophilia, thrombocytopenia, neutrophilia, basophilia, non-regenerative anemia are the most common clinical hemogram findings. Biochemical tests may show increased liver enzymes, bilirubinemia, and azotemia.

Thoracic radiographs can generally help interpret the disease in advanced stages, but they are not useful for diagnosis on their own. Findings such as dilation of the pulmonary arteries, abnormal pulmonary patterns, and changes in the shape of the heart may

be observed. The pulmonary parenchyma should be monitored, especially for fluid leaks and nodules. If right heart failure (R-CHF) is present, peritoneal and pleural effusion may be seen. In addition, some asymptomatic dogs may not show clinical signs despite having a high adult parasite load in the heart. (C.A. Calvert et al.1988)

Ultrasound is often useless except for monitoring nonspecific findings. Ascites and pulmonary edema due to heart failure due to right pulmonary artery occlusion can be monitored with ultrasound.

In some cases, parasite larvae may be encountered incidentally. These are parasites that have not reached the target organ, the heart, but have migrated to other tissues and organs. Microfilariae may be seen incidentally in urine tests, pathological findings caused by larvae may be detected in eye examinations, or parasites may be encountered incidentally in cytological or histopathological examinations of samples taken from organs (Perles, L et al.2024; Weiner, D. J. et al.1981). In this case, the patient should be tested parasitologically in its entirety.

5. Treatment and Protection Methods

Different goals may be desired in the treatment of *Dirofilaria immitis.* This is completely shaped by the physician's opinion, the patient's owner's opinion, the patient's parasitemic condition and the patient's financial situation. The general aim of the treatment is to eliminate the adult worm, microfilariae and Wolbachia bacteria. However, the high cost of some drugs, the lack of drug application opportunities, low or high parasitic load in the patient, and the patient's parasite stage (microfilariae, adults, larvae) may cause the treatment protocol to change.

The most important trump card against *D. immitis* infection is not to catch the disease. The terms "prophylaxis" and "precaution" are used for this. For this reason, protection methods against mosquitoes are applied. Primary protection methods include not traveling to endemic areas during periods when mosquitoes are active and providing protection against mosquitoes with mechanical barriers such as mosquito nets for dogs kept indoors. Annual veterinary visits and blood screening against *Dirofilaria immitis* are of great benefit, if you are in an endemic region, these tests should be performed twice a year.

In order to facilitate the treatment and control of the disease, patients are classified into two groups according to the risk of thromboembolism. These two groups, called “Low risk” and “High risk” patients, are separated according to the patient’s symptoms and clinical findings. The low risk group includes those without symptoms, those with normal radiological thoracic images, those with low antigen levels or those who are antigen negative but have microfilariae, and those who do not see adult worms on echocardiography. All conditions must be met. The high risk group is the group with a high thromboembolic risk and must meet at least one of the following conditions: symptoms related to the disease (coughing, swelling in the abdomen, etc.), abnormal thoracic radiography, high antigen level, adult worms seen on echocardiography, and already having the disease (L. Venco et al. 2004).

If they are in a high-risk group, exercise restriction should be applied to patients, thus cardiopulmonary circulation is increased and pulmonary hypertension is reduced. Drugs applied to kill microfilariae and larvae against D. immitis infection are called microfilariacides. For this purpose, the drug group called macrocyclic lactones is used. Selamectin, ivermectin, eprinomectin, milbemycin oxime and moxidectin are some of the frequently used drugs in this group (Savadelis, M. D. et al. 2017). It is recommended to use it at 30-day intervals, especially during mosquito seasons (Jacobson LS, DiGangi BA (2021);Roger K. Prichard. 2021). These drugs can be used as “Spot on” from the nape of the neck, as an injection or orally, depending on the commercial preparation. Some moxidectin preparations are long-lasting and can be used at wider intervals. In some regions of the USA, microfilariae resistance to these drugs seems to have begun and higher doses are being used. For this reason, finding new drug molecules is important (Roger K. Prichard.2021).

An integral part of the treatment is the elimination of Wolbachia bacteria. The mutualistic effect of this bacteria with the parasite ensures both the proliferation and development of the parasite (Mark J. Taylor et al. 2005). Therefore, antibiotic treatment is indicated in the presence of microfilar or adult parasites. Doxycycline is the more preferred antibiotic and is administered at a dose of 10 mg/kg twice daily for 28 days (Geary, T.G. 2023). It has been observed that the use of doxycycline and ivermectin reduces oxidative stress in addition to treating the parasite (Milan Rajković et al. 2023).

Treatment against adults of D. immitis in the heart is done with arsenic-containing drugs. These drugs are called “adulticide” drugs. Melarsomine dihydrochloride is the only approved and effective adulticidal drug. It is administered intramuscularly into the epaxial lumbar muscles (between L3-L5) at a dose of 2.5 mg/kg. It kills 90% of adult male parasites and 10% of females in a single dose. It is desired in the treatment not to kill them all at once but to kill them gradually, thus reducing the risk of thromboembolism and shock. For this reason, it is recommended to apply in 3 doses within the framework of certain protocols. (Geary, T.G.2023)

Supportive treatment is of great importance in the treatment. Dead adult parasites encounter a severe immune response by the body. This can cause shock and thromboembolism. Glucocorticoids (anti-inflammatory doses) and sodium Heparin are also used to minimize these risks. Glucocorticoids are used for a certain period of time and should be terminated by decreasing the dose in a controlled manner called “tapering”. If congestive heart failure occurs, diuretics, especially Furosemide, can be used. Heart medications (e.g. Digoxin, Pimobendan) can be used to reduce the risk of atrial fibrillation. Fluid therapy is indicated in cases of dehydration. (American Heartworm Society. (2020))

According to the guidelines determined by the American Heartworm Society, the treatment protocol is recommended as follows: After the first microfilariae application, Doxycycline is applied twice daily at a dose of 10 mg/kg for one month. Among the glucocorticoids, prednisolone is started at an anti-inflammatory dose of 0.5 mg/kg and the dose is reduced weekly by tapering. At the end of this period, the body is rested for one month and at the end of this second month, the first adulticide application is made together with the microfilariae application and prednisolone is started again and tapering is started. At the end of the third month, adulticide is applied again for two consecutive days after the microfilariae application and prednisolone is used again by reducing the dose for one month. Then, the animal is examined for microfilariae and in case of negativity, microfilariae checks are made after 6 months. In case of microfilarial positivity, microfilaricide application is performed and the patient is examined again for microfilarials after 4 weeks (American Heartworm Society.2020; Geary, T.G.2023).

Surgical removal of adult parasites from the heart is preferred especially in patients with high adult parasite load and high risk of caval syndrome (R.B. Atwell, I.B.J et al.1988). In these patients, parasites can be found and removed in large numbers in the right heart chamber and caudal vena cava. The locations of the parasites should be determined with echocardiography before and during the operation. This operation, which has very low intraoperative mortality with correct technique and application, requires high skill and technical equipment. Therefore, it is recommended that it be performed only by surgeons who are professional in this field (K. Ishihara et al.1990).

6. Zoonotic risks

Dirofilaria immitis is a parasite whose final host is dogs. However, it can also be transmitted to humans by mosquitoes carrying its larvae biting humans, and although it cannot become an adult, it can cause pathological problems. Although human infections are mostly coincidental, the increase in the number of cases reported in recent years has made the importance of this parasite in terms of public health more visible (Eroğlu, F. (2017)). Humans can be infected with the larval form (L3) as a result of being bitten by an infected mosquito. However, since humans are not a suitable final host for this parasite, D. immitis usually cannot reach adulthood and does not form microfilariae. Despite this, significant pathological effects can develop in the tissues where the larvae reach. Pulmonary Dirofilariasis, the form caused by the parasite settling in the lungs through the circulation, is most commonly seen. The body develops a granulomatous reaction to this foreign structure, and the resulting lesion is usually seen radiographically as small, round nodules. These lesions are often confused with lung tumors and may result in lung biopsy. In addition, nodules formed by the settlement of larvae in the eye, skin, testicles and various organs have been reported (Weiner, D. J. et al.1981; Aykur, M. et al.2021).

Diagnosis is usually made by histopathological methods, therefore lung lesions are detected by methods such as Computed Tomography/ Radiography and surgically removed, and in cases seen in other organs, samples taken from these organs are examined.

It is more frequently reported in humans in countries in the Mediterranean basin (Turkey, Italy, Spain, Greece), America, and countries on the Black Sea

coast (Russia, Ukraine). It is striking that these countries are regions where mosquitoes that carry the parasite are predominantly found. In a study conducted in Romania and Moldova, serological tests performed on blood samples taken from humans revealed seropositivity for D. immitis antibodies at a rate of up to 13% (L. Ciuca et al. 2018). High mosquito population, hot and humid climate conditions, abundance of stray dogs, and increased diagnosis rates due to increased diagnostic methods are all contributing to an increase in human Dirofilariasis cases (Eroğlu, F. (2017)).

For all these reasons, the importance of veterinarians is increasing due to their informing the public and patient owners and their preventive medical practices for animals.

Conclusion

Dirofilaria immitis continues to be an important parasite in veterinary medicine and public health due to its serious pathogenic effects on the host and its zoonotic potential. In this study, the biological characteristics, life cycle, epidemiology, pathogenesis, diagnostic methods and treatment protocols of the parasite are discussed in detail in the light of current literature. Especially in recent years, the increasing domestic animal population, climate changes facilitating the spread of mosquito vectors and the prevalence of subclinical infections are the main factors that make the disease difficult to control. The fact that veterinarians in the field may miss diagnoses of this parasite and that patient owners are not sufficiently informed about protection methods also causes the disease to become permanent in endemic regions. Although developments in diagnostic methods, especially ELISA and PCR techniques, play an important role in revealing subclinical infections, it should not be forgotten that false negative results may be obtained in some samples. Therefore, it is important not to limit the diagnosis to a single test and to evaluate clinical findings, laboratory tests and imaging methods together. Although treatment protocols have been developed, their applicability to every patient may be limited. In addition to adulticide and microfilarial drugs, antibiotic treatments targeting Wolbachia bacteria increase treatment success. However, the most effective approach to combating the disease is still preventive medicine practices. Monthly antiparasitic applications and vector control play a key role in breaking the infection chain. In terms of public health, the zoonotic potential of D. immitis is becoming more apparent every year. Therefore, not only veterinarians but also public health authorities need to raise awareness of D. immitis infection and create integrated control strategies, and it is recommended that the effects of climate change on the spread of the disease be investigated in more detail and on a larger scale.

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