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Canine Heartworm Disease

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Introduction

Canine heartworm disease is a very complex multisystemic disorder. The primary lesions involve the cardiac and pulmonary systems; however, it is not unusual for the hepatic, renal or even nervous systems to be involved. Since 1850, when heartworm disease was first described, it has become a major concern in canine medicine.

Distribution and Incidence

The incidence of canine heartworm disease has steadily increased through the years. Today, there are enzootic foci on nearly every continent. Originally a disease of warm coastal regions, unrestricted movement of infected dogs is held responsible for the spread of the disease to more temperate climates. In the United States there are now four enzootic regions. The first region extends along the Atlantic and coastal area, from Massachusetts to east Texas. This area includes the states with the highest prevalence of infection: Louisiana, Mississippi, Alabama, and Florida. At one time, infection rates in these states ranged from thirty to greater than fifty percent of the animals tested. Preventative programs have resulted in a decline of these numbers in recent years. Another enzootic focus engulfs the large number of states within the Mississippi River Valley, including Tennessee and Arkansas and extending north through Kentucky, Illinois, Indiana, Ohio, Missouri, Iowa, Minnesota, Wisconsin and Michigan. In another five to ten years, it is expected that this focus will have moved to include many of the states to its west. Naturally acquired infections have already been reported in Nebraska, Kansas, and Colorado.

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Hawaii can be included in the well established enzootic regions of the United States, and a relatively new focus in northern California has emerged since the beginning of the 1970's.

Etiopathogenesis

Heartworm disease is the result of infection with the nematode Dirofilaria immitis. The adult worm lives within the right ventricle of the heart and pulmonary arteries. D. immitis is the longest of the Dirofilaria genus. The adult female can reach lengths of 250-310mm. The smaller male measures 120-200mm. The female is viviparous, releasing microfilariae into the host's circulation. The parasite requires an intermediate host to pick up the microfilariae from the bloodstream and over sixty species of mosquitoes are capable of acting as this intermediate host. The mosquito appears to be the only arthropod capable of supporting growth of the microfilariae. Research attempts to infect other arthropods, including the flea, have been unsuccessful. The mosquito ingests the microfilariae with its blood meal. By day thirteen, the microfilariae have molted twice and developed into the infective third stage larvae. The larvae migrate to the proboscis and cephalic spaces of the mosquito, and are now prepared to infect the host.

Canines, both wild and domestic, appear to be the definitive hosts of the heartworm. Incidental necropsy findings have revealed adult worms in a large number of other mammals, including man. However, these infections are rarely patent, and usually consist of a single adult worm or a few infertile worms in a location outside of the heart. Microfilariae positive infections have been documented in the domestic cat, fox, sea lion, and ferret. None of these animals represent a serious concern as a reservoir host. Among the domestic canines, there is no evidence of a breed or sex predilection. Length of hair coat is not important either. Statistics have shown that the deciding factor is depend-
ent only on exposure risk. Outdoor and working dogs have a 3-6 times greater infection rate than the household pet.2

The host becomes infected when an infective mosquito, acting as the vector, deposits the third stage larvae onto the skin of the host. The larvae later enter the host through the wound created by the mosquito. They remain in the subcutaneous tissue near the site of entry for the first 21 days. After molting into the fourth larval stage, they migrate through the abdomen and thorax of the host. Around day 70-80, the last molt occurs; this is the time when the first worms have reached the heart. By day 90-120 all of the immature worms have reached their destination. Only about 40 percent of the larvae entering the host actually develop into adults.1 Maturation and patency usually develop 5-7 months after infection.

Clinical Presentations

The majority of heartworm cases presented to a veterinarian are picked up by routine diagnostic testing. In these animals, the disease is mild and clinical signs are often absent. In animals with heavy worm burdens or more advanced disease, the clinical signs are usually explained by the pathological changes within the cardiovascular system of the lungs. The presence of the adult nematode within the pulmonary arterial system results in an intense inflammatory reaction of intimal proliferation. This response is unique to heartworm disease. The proliferative growth varies from papillary extensions to luxurious folding of the intima. Older lesions become more scarred and cobblestone in appearance. The results of the lesions are restricted vessel lumens and thickened walls. Fibrosis of both the intima and the media is more pronounced in the smaller arteries, and complete obstruction can occur. In advanced disease, the sum total of these changes causes a dramatic decrease in the cross-sectional area of the pulmonary arterial system and pulmonary hypertension. Dilation and hypertrophy of the right ventricle results from the pressure overload. Clinical signs become apparent as these cardiovascular changes progress.

Animals may present initially with a general loss of condition and a dry, harsh hair coat as a result of the metabolic stress. Chronic cough and hemoptysis are also common complaints. Auscultation is often normal; although an accentuated S2 and/or soft systolic murmur may be heard. Friction rubs may occasionally be present due to pleural adhesions caused by peripheral pulmonary hemorrhage. Mucous membranes may be pale due to both a depression anemia and perfusion deficiencies. As the severity of the disease condition progresses, cardiac insufficiency becomes evident. The animal becomes exercise intolerant and may experience syncope, tachypnea, and tachycardia. Auscultation at this point may reveal a systolic murmur associated with both the pulmonary and tricuspid valves. Worm-induced turbulence and dilation of the valvular annulus are believed to be responsible for the murmur. Severely diseased animals may present with signs of right-sided congestive heart failure: hepatomegaly, ascites, and a jugular pulse. As left-ventricular output drops from the low volume of blood passing through the hypertensive pulmonary system, the femoral pulse becomes weak. In very severe cases, peripheral cooling and extremity edema may be evident. These latter two signs are extremely poor prognostic indicators.

Diagnosis

The release of microfilariae into the infected host’s circulation should make the diagnosis of heartworm infection straightforward. Unfortunately, the picture is complicated by many other variables. First, 10-67% of infected animals do not have any circulating microfilaria.3 These cases are referred to as occult infections. The classical occult presentation is the result of microfilarial trapping within the pulmonary capillary system by antibody and leukocytes. Absence of circulating microfilariae also occurs with prepatent, unisex, and infertile infections. Second, the presence of microfilariae is not always indicative of adult D. immitis infection. A documented 4.5% of microfilariae positive animals have no adult worms.4 After natural mortality (approximately seven years) or adulticide treatment, microfilariae can remain in the bloodstream for up to 2 1/2 years.1 Microfilariae can also be transferred to uninfected animals by blood transfusion or placental transfer. Lastly, although D. immitis is the only filarial parasite which results in clinically apparent disease in the dog, another parasite, Dipetalonema reconditum. also produces circu-
lating microfilariae. Endemic to the same regions as the heartworm, *D. reconditum* uses the flea as its vector and lives within the subcutaneous tissue of its host.

Because of the enormous number of variables involved in heartworm infected animals, diagnostic tests have been developed for both microfilariae detection and serological evaluations. Each test available has appropriate applications, and associated advantages and disadvantages.

**Microfilariae Detection**

These tests are the simplest and the least expensive available. It is important to be aware of the following characteristics of microfilariae:

- Microfilariae are not present until 5-6 mo post infection
- The numbers of microfilariae present do not correlate with the number of adult worms present
- The numbers of microfilariae in any one host show both seasonal and daily cyclicity. Increased numbers are present during the spring and summer, and in the late afternoons and evenings
- Some infected hosts show no circulating microfilariae
- The microfilariae of *D. immitis* must be differentiated from those of *D. reconditum*.

Wet mount: The technique of using a drop of peripheral blood on a glass slide and observing under a microscope is only dependable in infections with a high number of microfilariae. It does not allow the assessment of the morphology of the microfilariae, but can give a good idea of the motility involved. This should not be used as the sole means of diagnosing heartworm infection.

Microcapillary tube: This method makes use of a sample of blood within a microhematocrit tube. Once again, microfilariae numbers must be high, and assessment of morphology is not possible. The tube is viewed under the microscope, focusing up and down in the region above the buffy coat. *Dipetalonema* microfilariae tend to migrate well up into the plasma; *Dirofilaria* tends to remain just above the buffy coat. This test is useful as a screening measure if the blood has been drawn for other tests, but should not be relied on for a diagnosis.

Concentration techniques: The most commonly used tests in this category are the filter tests and the modified Knott’s test. Concentration methods are 10-15% more sensitive than the previous exams, and 50-90% more accurate. These are the most frequently used tests in veterinary clinics today. They are very useful in routine yearly exams before beginning a prevention program, as well as for the initial exam of a suspected heartworm diseased animal.

The filter tests make use of a 1 ml sample of whole or EDTA blood. This sample is placed in 9 ml of a lysing solution; the lysed sample is run through a filter chamber, and flushed with 10 ml of water. Depending upon the set purchased, a dye may be used on the filter after it has been placed on a glass slide. The sample is read using a microscope. To avoid false positives, care must be taken not to contaminate the lysing solutions with microfilariae positive blood, and chambers should be cleaned well between uses. False negatives can occur if improper filters are used.

The modified Knott’s test is the best for examining the morphology of the microfilariae. Although it requires a longer period of time, sensitivity is equal to that of the filter tests and it is less expensive. One ml of whole blood is mixed with 9 ml of 2% formalin and centrifuged for 5-8 minutes. The supernatant is discarded and the sediment is stained with methylene blue and viewed microscopically. Adequate centrifugation is essential to prevent the loss of the microfilariae with the supernatant.

**Serological testing**

Serological exams were developed to identify the occult heartworm infections. They can be extremely helpful if used properly and in the correct situations. The accuracy and sensitivity of detecting infection varies greatly among the different tests available. The results are not absolute and should be used in conjunction with history, clinical signs, and other diagnostic aids. These tests are generally more expensive and involved than the microfilariae detection tests, and are most useful following a negative microfilariae detection test on a suspect animal.

Indirect Fluorescent Antibody: (e.g. Track XI) This test detects circulating host antibody to the microfilarial cuticular antigen. It is
useful in detecting the true occult infections. It will not detect infections where microfilaria were never produced, as occurs with single sex, prepatent, and single worm infections. Eighty-five to ninety percent of the immunological occult infections are positive by this test. The exam is an involved procedure, and not offered in most labs.

Enzyme-linked Immunosorbant Assays: Two different types of ELISA tests have been created to assist in the diagnoses of heartworm infection. The predictive value of each of these is extremely different, so they will be discussed separately.

The first ELISA applied towards diagnosis detected circulating antibody to the adult *Dirofilaria*. Most of these tests (e.g. Dirotect®, Dirokit®) have since been withdrawn from the market. Their accuracy was extremely low, and cross-reactivity to both *D. reconditum* and intestinal nematodes was very common. Research showed values of 47% false positives, and 30% false negatives. They did have some value in detecting prepatent or immature infections, where antibody may be increased, and antigen not yet detectable.

The newest ELISA available detects the circulating adult *Dirofilaria* associated antigen. These tests (e.g. Filarochek®, Dirochek®, CITE®) are extremely sensitive, specific, and accurate. Cross-reactivity is not a problem. One trial showed only 4% false negatives, and 2% false positives. The test can be run on fresh or frozen serum samples and shows 95% sensitivity in animals with a burden of five or more worms. This test has quickly become the serological test of choice. It shows positive results as early as six months post infection, and twelve weeks after effective adulticide treatment antigen levels are nondetectable. The test is also showing great promise as a prognostic indicator. Two fold dilutions of the patients serum with physiological saline can be used to calculate a titer. This titer is used to predict the relative worm burden and identify the dogs with the greatest risk of pulmonary embolic disease after adulticide treatment. This test can also be used to detect circulating antigen in the less common hosts of *D. immitis* such as the cat, ferret, sea lion, or any other suspect animal.

After establishing the presence of heartworm infection, treatment of the animal should be strongly encouraged. Untreated animals serve as a reservoir of infection for other animals. The treatment regime can be divided into five steps:

1) Pretreatment Evaluation
2) Stabilization: Supportive /symptomatic care of existing clinical conditions
3) Adulticide
4) Microfilaricide
5) Prophylaxis

Pretreatment evaluation: is important to establish the health status of an animal prior to adulticide treatment. The recommended minimum data base varies greatly from source to source. A complete history and thorough physical exam are essential. The physical exam should closely evaluate the cardiopulmonary system. A CBC and serum chemistry profile are recommended for older patients over five years, as well as any showing clinical signs. A urinalysis has also been advised. These latter tests, although not predictive of possible complications, establish the presence of concurrent disease conditions. Thoracic radiographs are strongly recommended for clinical cases. The degree of radiographic change has a direct relationship to the duration and severity of infection. Radiographs can provide a clinician with valuable prognostic information.

Stabilization of the patient's condition prior to the adulticide treatment is important, even if treatment must be delayed for several weeks. Animals may present with severe concurrent disease conditions on the pretreatment evaluation. These clinical signs may be a direct result of advanced heartworm disease, or exist as a separate entity.

Adulticide treatment can begin immediately after stabilization of the patient. Two drugs have been used as adulticides, levamisole and thiacetarsamide. Levamisole is not approved for this use, and is not dependable. Adult female worms are very resistant to its effects. Thiacetarsamide is the better choice for treatment. Thiacetarsamide is approved for use as a *Dirofilaria* adulticide. It is in no way an ideal drug. Experimentally, worm kills have been around sixty-three percent; only forty percent of the dogs treated were completely cleared of adults. The immature and female worms show
some resistance to the drug. The treatment protocol involves four intravenous injections at intervals not less than 6-8 hours, or greater than 15 hours. Care must be taken not to inject the drug perivascularly or severe skin sloughs can result. An injection of 2.2 mg/kg is given BID for two consecutive days. The animal may be usually hospitalized for 1-2 weeks following treatment for observation.

Adverse reactions may be seen with adulticide treatment. Toxic reactions to thiacetarsamide occur infrequently. As an arsenical compound, thiacetarsamide is excreted by the kidneys, gut, and liver. It can produce both hepatotoxicity and nephrotoxicity. Clinical signs include vomiting, lethargy, anorexia and icterus. Vomiting after the first dose is not uncommon and usually can be controlled by feeding 30 minutes prior to the injections. If vomiting persists, or other signs occur, treatment should be aborted. After restabilization, the animal can be retreated in 4-6 weeks. Toxic reactions following the second treatment are rare. No diagnostic test has been found which accurately predicts acute toxicity. Liver enzyme values are not predictive.

Liver sparing drugs such as choline, methionine, or inositol have no value. One source indicated the presence of bilirubinuria may be a clue to impending toxicity, and should be evaluated before each injection. Aborting the treatment, and supportive care is usually sufficient to correct the toxicosis.

Pulmonary thromboembolism occurs as a sequelae of adulticide treatment. It occurs most commonly 7-17 days post treatment, but clinical signs of embolization been reported from 5-30 days post adulticide. These signs include cough, dyspnea, pulmonary crackles, fever, and tachycardia. Animals showing radiographic evidence of severe pulmonary parenchymal disease are more likely to experience clinical signs of thromboembolism. If signs occur, prednisone should be administered at a dose of 1-2 mg/kg until clinical and radiographic signs have resolved. Corticosteroids should only be used if signs of thromboembolism occur. They will decrease the efficacy of thiacetarsamide, and more seriously, may exacerbate the degree of arterial disease and promote thromboembolism, periarterial fibrosis, and decreased pulmonary blood flow.

Antibiotics, bronchodilators, and aspirin may also be valuable as adjunct therapy for pulmonary thromboembolism. Aspirin is used in animals with radiographic evidence of severe pulmonary arterial disease. It appears to block the ongoing pathogenesis of endothelial damage and permits partial regression of lesions in the presence of adult heartworms. It should not be used routinely for heartworm infected animals. A dosage of 7 mg/kg for 13 weeks prior to adulticide treatment and 3-4 weeks following treatment has been recommended. The animals should be observed closely for gastrointestinal bleeding, and concurrent use of cimetidine or oral protectants is advisable.

Microfilaricide is given 4-6 weeks after the completion of adulticide treatment. There are several drugs available for use as effective microfilaricides.

Dithiazanine is the only approved microfilaricide available. It is administered orally at a dosage of 7-11 mg/kg for seven days. If microfilariae appear on a recheck following treatment, a dosage of 11 15 mg/kg is used for an additional seven days if no signs of toxicity occur. Dithiazanine is a cyanide dye. Toxic effects include vomiting, diarrhea, and anorexia. Feeding a meal prior to treatment may prevent vomiting. Clients should be warned the vomitus and feces from treated animals will stain fabrics.

Levamisole, although not approved, has been used as a microfilaricide. Administered orally at a dosage of 10-11 mg/kg, SID for 1-2 weeks, it is as effective as dithiazanine. Animals should be rechecked after one week of treatment. If toxic signs such as vomiting, lethargy, stiffness, or nervousness occur, treatment should be stopped. Levamisole has a low margin of safety, and the above dosage should not be exceeded. Dividing the dosage into a BID treatment may prevent vomiting, without altering efficacy.

Ivermectin is the most recent introduction to the microfilaricide line. Although not yet approved for this use, it is very popular among practitioners. One oral dose at 50 mcg/kg is 99.9% effective in clearing an animal. If two consecutive rechecks prove positive, surviving adult worms should be suspected. Toxic reactions to ivermectin are very rare, but occur more frequently with high numbers of microfilariae. Collies have also shown an increased sensitivity at this dose, presenting with an anaphylactoid reaction. Its use in this breed should be avoided.

Prophylaxis should begin immediately after clearance of the microfilaremia if exposure to infected mosquitoes is possible.
Heartworm disease can be prevented. Prevention is much safer and more effective for the animal than treatment. Most prevention programs today make use of either diethylcarbamazine or ivermectin. Both of these drugs are approved as preventatives, and are very safe and nearly 100 percent effective if used properly.

Prophylaxis should begin with the mosquito season, and continue for two months after the seasons end. In warm climates, prophylaxis should be continued throughout the entire year. Animals should be checked for heartworm infection prior to beginning prophylaxis each year, or every six months if year round prevention is used. Testing is not necessary for animals less than six months of age, since patency could not yet be present. Pups can begin prevention therapy at 6-9 weeks of age.

Diethylcarbamazine (DEC) is administered at a dosage of 6.5 mg/kg orally on a daily basis. DEC can only be used in amicrofilaremic animals. Its use in microfilaria positive animals may result in anaphylaxis, with DIC, shock, and death in 5-20% of the reacting animals. If an animal on DEC is discovered to be microfilaremic, the drug should be continued on a daily basis during treatment. However, if no DEC has been given for several days do not reinstitute the therapy. Its use to prevent reinfection during the treatment of occult disease is safe. Side effects in amicrofilaremic dogs are very rare. Vomiting may occur infrequently.

Ivermectin can be used at a dosage of 6 mcg/kg orally once a month. At this dosage it is an effective preventative but not a microfilaricide. Toxic reactions are very rare, even in the collie breed at this dosage. It can be given to microfilaremic animal without adverse reactions. This is a great advantage in animals where the heartworm infection is asymptomatic, and age or concurrent illness makes treatment a great risk. The adult worms will die naturally, while the animal is protected from reinfection. It is important to remember that these animals are still sources of infection.

References


