

# All You Need to Know About Heartworm Disease

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## INTRODUCTION

Dirofilariasis or heartworm (HW) disease is an important and common parasitic disease of dogs and to a lesser degree the cat. Other species (such as ferrets and wild canines) also can be infected. *Dirofilaria immitis* is a large (12 - 30 cm), string-like parasite that resides within the pulmonary arteries but the parasite may be found in the right ventricle or right atrium as well. at necropsy. Adult heartworms can live up to 5 years in dogs but probably less than 3 years in cats. Males are up to 16 cm long with a “curly” end; females are longer, up to 30 cm. Young female worms are not only large, but the most resistant to adulticidal chemotherapy. Mature adults produce microscopic offspring that circulate in the blood (patent infection). *Microfilaria* can survive up to 2 years though circulating microfilaremia in infected cats is very brief and many dogs become amicrofilaremic. Should *microfilaria* be ingested by a mosquito, these can develop into infective larvae or L<sub>3</sub> stage, provided the daily average ambient temperature is not too cold (above 57 degrees F, ideally more than 64 degrees). When an infected mosquito bites another animal, infective larvae are transmitted to the new host. Both dogs and cats can be infected experimentally by injection of infective larvae. Cats are a susceptible but resistant host. In natural settings, even in epidemic areas, where nearly 100% of unprotected dogs are positive for HW infection, only about 20% of unprotected cats may be positive. This demonstrates the relatively greater natural resistance of cats to this disease (as well as mosquito host preference); however, when infected with heartworms, the cat often manifests more severe clinical signs than in dogs.

## LIFE CYCLE

The life cycle of the heartworm that takes approximately 200 days under optimal conditions. Domesticated and wild canine species constitute the definitive hosts. The cat is more resistant, and less frequently affected with heartworm infection.

### Mosquito and Pre-pulmonary Phases:

- A mosquito ingests *microfilaria* (L<sub>1</sub>) during a blood meal from a host with a patent infection
- Larvae moult within the mosquito to the L<sub>3</sub> stage.
  - This phase requires about 15-20 days.
  - Only infective L<sub>3</sub> larvae can develop further into adult heartworms
  - this requires the intermediate host.
- The mosquito deposits infective larvae during a blood meal.
  - The larvae penetrate into the subcutaneous tissue and moult twice L<sub>3</sub> to L<sub>4</sub> and L<sub>4</sub> to L<sub>5</sub>
    - This takes approximately 60-70 days
- Commonly used heartworm preventatives, including diethylcarbamazine (Filarabits®), ivermectin (Heartgard®, Iverheart®), milbemycin (Interceptor®), and moxidectin (Pro-Heart®) are active during the subcutaneous phase of infection.
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### Pulmonary infection:

Viable L<sub>5</sub> migrate and penetrate systemic veins where they are swept in the blood stream and to the peripheral pulmonary arteries. Here the parasite grows and matures. Pulmonary embolization of larvae occurs relative to the degree of pulmonary flow. Therefore, the caudal lobes are most severely affected by disease in most situations. Immature adults grow back towards the main pulmonary artery and right ventricular outflow tract.

- Adult filaria can attain lengths of up to 30 cm (females).
- Adult parasites are relatively hardy, but can be killed by arsenic containing compounds such as melarsamine (Immiticide)
  - Long-term exposure to ivermectin also may kill adult parasites, but the time-course for worm death is long (often > 2 years), and continued injury to the lung and pulmonary vasculature may occur during this interval.
  - Adult parasites injure the lung and pulmonary arteries and spontaneous or induced death of mature heartworms incites an acute pulmonary reaction

- In cats the reaction can be severe and fatal

#### Adult Infection:

- Adult female parasites can produce thousands of microscopic offspring or microfilaria.
- An infection is said to be “patent” once adults begin producing detectable microfilaria.
  - This generally occurs between 184 to 210 days into the life cycle.
  - Microfilaremia is transient in cats and infrequently detected in clinical patients.
  - Some canine heartworm infections also are microfilaria negative at the time of diagnosis. This condition historically has been termed “occult” heartworm infection.
  - Circulating microfilaria can be killed by a number of drugs including ivermectin and milbemycin.

### CLINICAL SYNDROME

There is no specific age or breed predilection, although dogs < 7 months cannot conceivably be diagnosed as having HW disease. It is possible for young dogs to be microfilaria positive owing to transplacental infection or a microfilaria positive blood transfusion but both are considered quite rare. Large breed, short-haired, male dogs are at greater epidemiologic risk. Environment is important since areas which abound with mosquitoes (beaches, lakes, and coastal states) will be endemic for HWD.

Based on clinical serologic survey data and results of reported retrospective studies there is no age or breed predisposition to *D. immitis* infection or exposure in cats. Males have been shown to be more susceptible to infection in some clinical and experimental studies. This sex predisposition has not been supported by recent serologic surveys however these surveys report exposure and not mature infection. A recent necropsy study from Beaumont Texas reported that more males than females harbored adult heartworms but this difference was statistically insignificant. Interestingly that same study reported that only 50% of the cats in which adult worms were found at necropsy were antibody positive. Cats that have outdoor exposure are at increased risk of infection with any exposure to the outdoors increasing the risk of exposure by a factor of two. It is important to emphasize that heartworm disease has been diagnosed in cats which the owners report as living strictly indoors.

### History

Many dogs with dirofilariasis are asymptomatic (HW infection) and diagnosed on routine HW screening tests. The symptomatic patient (HW disease) may present for any or all of the following historical complaints: Weight loss, anorexia, poor condition

- Exertional dyspnea, fatigue, coughing or hemoptysis
- Vomiting, syncope (fainting) or collapse with exercise
- Signs of right-sided CHF noted by the owner (weakness, weight loss, swollen, fluid-filled abdomen)
- Red-colored urine (not from blood but from hemoglobin pigment) - this is a sign of caval syndrome
- Sudden death after a brief illness or under anesthesia

Cats can be presented for peracute or chronic signs or be completely asymptomatic. The acute syndrome is commonly associated with acute respiratory compromise secondary to severe pulmonary thromboembolism and frequently results in death. Any cat that dies suddenly in an area know to be endemic for heartworm should be evaluated (meticulous necropsy) for evidence of *Dirofilaria immitis* infection. Historical complaints in cats with chronic signs of heartworm disease are typically referable to the cardiopulmonary system (coughing, dyspnea), gastrointestinal system (vomiting unrelated to feeding), but may be quite vague (lethargy, partial anorexia and weight loss). Vomiting and respiratory signs seem to be the predominant signs in chronic disease.

Physical examination may reveal a normal animal or any of the following clinical signs:

- Weight loss, poor condition or Depression
- Dyspnea, tachypnea, increased bronchial lung sounds and/or pulmonary crackles
- A loud or split (inconsistent) second heart sound
- a systolic murmur of tricuspid regurgitation
- Arrhythmias may be ausculted
- Distended jugular veins or prominent jugular pulsations indicate right-sided CHF
- Collapse, TR, associated with shock, hemoglobinuria, and DIC is suggestive of caval syndrome

Physical examination of cats with heartworm disease is frequently unremarkable. The presence of increased bronchovesicular sounds is one of the more common abnormalities reported but is a very nonspecific. Auscultation of a murmur or gallop rhythm is very unusual in cats with heartworm disease and should increase the

clinician's suspicion of primary and secondary cardiac diseases including idiopathic cardiomyopathy, thyrotoxic or hypertensive heart disease and less commonly valvular heart disease.

## LABORATORY TESTS

Routine diagnostic tests are often done in HWD. Some of these are very useful in staging the severity of disease, while others are of limited value.

### Radiography

The history, clinical examination, and thoracic radiographs provide the most useful information about the status of a heartworm infection. Results of radiography may be normal. Abnormal thoracic radiographs may be found in either asymptomatic or ill patients. The following represent the salient radiographic features of moderate to severe HWD

- Right ventricular enlargement
- Bulging of the main pulmonary artery or an inverted “D” appearance to the cardiac silhouette
- Centrally enlarged, tortuous, and blunted left and right lobar pulmonary arteries
- Patchy, ill-defined, increased densities compatible with alveolar infiltrates due to infarction, edema, or eosinophilic pneumonitis; increased interstitial densities related to pneumonitis or fibrosis. Caudal lung lobes are usually more severely affected, especially the right-caudal lobe
- Pleural effusion is rare but can occur

Thoracic radiography is one of the most useful tests available for the evaluating suspected *D. immitis* infection in the cat. It is important to not only know the radiographic features of dirofilariasis but the more important differential diagnosis as well. The most commonly reported findings in cats with heartworm infection include prominent, enlarged pulmonary arteries that may or may not be notably blunted or tortuous. The caudal lobar arteries usually show the earliest radiographic changes with the right and left being equally affected. The radiographic changes are best appreciated on the dorsoventral or ventrodorsal views. Evaluation of the pulmonary arteries may be hindered by the presence of significant pulmonary parenchymal disease. Therapy for the pulmonary parenchymal disease may be necessary before diagnostic thoracic radiographs can be obtained. It is uncommon to see significant alterations in cardiac size or shape and signs of congestive heart failure are quite uncommon. Chylothorax has been described in association with both experimental and naturally occurring *D. immitis* infections in the cat. Chylous pleural effusion warrants further pursuit of a diagnosis of feline dirofilariasis.

### Echocardiography

Routine echocardiography is not required in diagnosis or management of heartworm disease in dogs. Echocardiography is most useful for evaluating the patient with heart failure for diagnosing caval syndrome and eliminating the diagnosis of other common causes of right heart failure (pericardial disease and dilated cardiomyopathy). In severe disease the echocardiogram typically documents RV and right atrial enlargement, flattening of the ventricular septum, and dilated main and lobar pulmonary arteries. Adult parasites appear as parallel, linear, echodensities with a central hypoechoic zone. Ultrasound is more helpful in smaller animals as the parasites are located more centrally. In the caval syndrome, worms are evident in the tricuspid orifice and right atrium.

In contrast to dogs, echocardiography is very helpful in the diagnosis in cats because laboratory tests can be negative in the setting of infection. Numerous reports and abstracts have documented the diagnostic utility of echocardiographic in cats with heartworm disease. Sensitivities ranging from 34-100% have been reported suggesting that in greater than 50% of cases worms can be visualized within the cardiac chambers or pulmonary arteries. It is imperative that adequate visualization of the entire right heart, bifurcation of the main pulmonary artery and the proximal portion of the right pulmonary artery be obtained. Most worms are seen in the pulmonary arteries and appear as parallel hyperechoic structures typically about 0.7-1.2 mm thick and separated by approximately 0.5-1.0 mm most commonly described as resembling a bright “equals (=) sign”. The length, however is variable reflecting the angle at which the worms are aligned relative to the echocardiographic imaging plane. Determination of the exact number of worms is often quite difficult. Importantly, echocardiography is very helpful in establishing or refuting a diagnosis of primary cardiac disease.

### Electrocardiography

The EKG is of limited value in this disease. The ECG is normal except in severe HWD when widening of P-waves, RVH pattern, and right axis deviation occur. If an arrhythmia is detected by auscultation, an ECG should be done as atrial and ventricular arrhythmias may be observed in advanced disease. In cats, although evidence of right ventricular enlargement is occasionally evident, the electrocardiogram is normal in most cats with heartworm disease. Significant axis shifts or dysrhythmias should increase the clinician's suspicion of primary cardiac disease.

### **Complete Blood Count and Serum Biochemistries**

Abnormalities seen on the CBC in HW infection can include eosinophilia but this is evident in less than 50% of cases; basophilia; and monocytosis. If this triad of findings is detected, always consider HW infection. It is emphasized, however, that the CBC are often normal. Mild normocytic, normochromic anemia, probably from chronic disease, is found in 30-35% of dogs. RBC fragments may be seen suggesting low grade disseminated intravascular coagulopathy. DIC occurs in severe cases (particularly in caval syndrome and with severe pulmonary vascular disease) Serum biochemical tests are normal except for protein changes and mild to moderate elevation of liver enzymes which are possibly related to congestion. Hyperglobulinemia is also very common in cats with HW infection. In cats abnormalities detected on routine blood work are fairly nonspecific. Complete blood counts often show a mild non-regenerative anemia and occasionally increased numbers of nucleated red blood cells. Eosinophilia is an inconsistent finding, even on serial samples. Experimentally, peripheral eosinophilia most commonly occurs 4-7 months post-infection and intermittently thereafter. If peripheral basophilia is noted in conjunction with eosinophilia, the a diagnosis of heartworm disease should be pursued. Hyperglobulinemia is one of the few commonly observed biochemical abnormalities.

### **Tests for Heartworm Infection**

Diagnosis of HW infection requires detection of circulating microfilaria or heartworm antigens in the dog. Antigen tests are the method of choice as many dogs do not have circulating microfilaria. A number of sensitive and specific antigen tests are available that detect the presence of heartworm antigens derived mainly from adult females. These tests vary in diagnostic methodology, but include simple single test kits and "batch" kits. The technology improves constantly, and some antigen tests can detect the presence of just one or two female adult parasites. Antigenemia is generally evident when worms are seven months of age; some tests may detect antigenemia in worms as young as 5 months of age. The competition among test kit manufacturers makes it difficult to identify a clearly superior test kit. Some kits are "semiquantitative" providing some information about relative worm burden. Careful attention to detail is important. Ambiguous test results are best followed up by sending the sample to an outside reference laboratory. It should be emphasized that regardless of test sensitivity and specificity, the positive predictive value of a test still depends on the prevalence of disease in the hospital population.

Several testing methods are available for detection of microfilaricidal infections in cats. The indirect fluorescent antibody test (IFA) detects host antibodies against microfilarial cuticular and somatic antigens. This test is commercially available only from Antec Labs (Farmingdale, New York; Irvine, California). Recent reports suggest that the IFA test is a highly specific and sensitive indicator of heartworm exposure detecting some infections as early as 1-2 months post infection. The ELISA test (Animal Diagnostics [BioClin], St Louis, MO; Heska Corporation, Fort Collins, CO) which detects antibodies (Ab) to heartworm antigen is quite sensitive. The Ag against which the Ab is directed is present in large amounts in the L<sub>4</sub> and L<sub>5</sub> stages and to a lesser degree in the L<sub>3</sub> stage. Recent studies using both tests to evaluate well characterized feline serum suggest they are quite specific even in the presence of heavy intestinal parasitism. A positive Ab test simply documents exposure while a negative test makes a diagnosis of feline heartworm disease less likely. There are however some cats with mature heartworm infection (positive ELISA Ag test or documented via necropsy or echocardiography) that have been Ab negative. This situation was thought to be quite uncommon however one study suggested this may occur in as many as 50% of adult infections. Antibody negative cats showing clinical signs typical of heartworm disease and in which other tests (radiography) support a diagnosis, deserve further evaluation. This additional evaluation might include an echocardiogram, an ELISA Ag test, additional Ab tests (perhaps using an alternative laboratory) and in select cases nonselective angiography. Circulating Ab are typically detectable within 2-4 months of exposure and the ELISA tests may remain positive for 9-12 months, even if a mature infection is not established. An in house ELISA test marketed by Synbiotics Corporation (Assure<sup>®</sup>/FH) and an immunochromatography format test (SoloStep<sup>®</sup>) marketed by Heska Corporation have been approved by the FDA.

The ELISA tests offered by Heska and Animal Diagnostic labs are considered quantitative with the intensity of the test correlating to some extent with the likelihood of mature infection. The results of Heska's test are reported in antibody units per milliliter (AbU/ml). Using these units a value less than 5 ABU would be considered a negative test, a value greater than 5 but less than 20 ABU/ml would be typical of exposure while a value greater than 20 ABU/ml would be common in cats with a mature infection. It is important to emphasize that these values are guidelines and do not represent definitive categories. The results of the Animal Diagnostics' test is reported as a titer (reported range is 1:70 to >1:5000) with a titer of 1:70 considered positive. The higher the titer the more likely it represents mature infection. In asymptomatic cats with a titer of < 1:120 only 1% had a positive Ag test. In symptomatic cats with titers <1:120 but greater than 1:70, 28% were Ag positive. In cats with titers greater than 1:3000, 78% were AG positive. Serial titers may be informative with increasing ABU concentrations or Ab titers suggesting sustained or ongoing infection. Due to the nature of the titering system a titer needs to change by a factor of four (4) to be considered significantly different.

The ELISA and ICT tests which detect circulating adult heartworm antigen (HWAg) are the most specific tests currently available to detect mature infections. Although the tests were originally marketed for use in the dog, the methodology used allows the tests to be used in any species. The antigen detected is a series of related acidic proteoglycans derived primarily from the adult female worm. Low worm burdens (less than 3 worms), all male infections or immature infections may result in false negative test results. When evaluating the results of an ELISA or ICT (HWAg) test in a cat; a negative test result does not rule out dirofilariasis, but a positive test is very strong evidence of heartworm infestation. Several studies (echocardiographic, experimental and necropsy) suggest that approximately 40% of cats with adult worms are Ag positive.

### Microfilaria tests

There is still merit in detecting microfilaria when an antigen test is positive. The following summarizes the key morphologic features of concentration techniques or wet mount smears. The modified Knott's technique provides good differentiation between microfilaria of *D. immitis* and other nonpathogenic species. Microfilaria of *D. immitis* must be differentiated from microfilaria of the flea-transmitted, subcutaneous, nonpathogenic worm, *Dipetalonema reconditum*. In mixed

Table 1		
Parasite Name	<i>Dirofilaria immitis</i>	<i>Dipetalonema reconditum</i>
Numbers	Few to large numbers	Usually small numbers
Motility	Undulate in one place	Move across the field
Morphology	Straight body, Button hook tail	
Head	Tapered	Blunt
Length	298-314 microns	264-298 microns
Width	6-7microns	5-6 microns
Width and morphology are considered best for discriminating between the two parasites.		

infections, it is likely that *D. reconditum* will be missed since these usually constitute less than 1% of the microfilaria present. Differentiation of larvae (microfilaria) can be made using a wet mount and Knott's test. In approximately 10 to 30% of dirofilarial-infected dogs (up to 50% in some areas), and in virtually all infected cats, microfilaria cannot be demonstrated; "occult" HWD. In some surveys up to 80% of cases of severe HWD are occult. Concentration techniques (Difil<sup>®</sup>, modified Knott's) can be performed in cats suspected of having heartworm disease but are often of little value as less than 20% of all infections are patent. Even in cats with circulating microfilaria, the low concentration and transient nature of the microfilaremia results in a large number of false negative test results. The sensitivity of the concentration tests may be improved by performing multiple tests and by using 5 ml of blood for each test rather than the standard 1 ml. Although the concentration tests have a very low sensitivity, a positive test establishes a definitive diagnosis (Table 1).

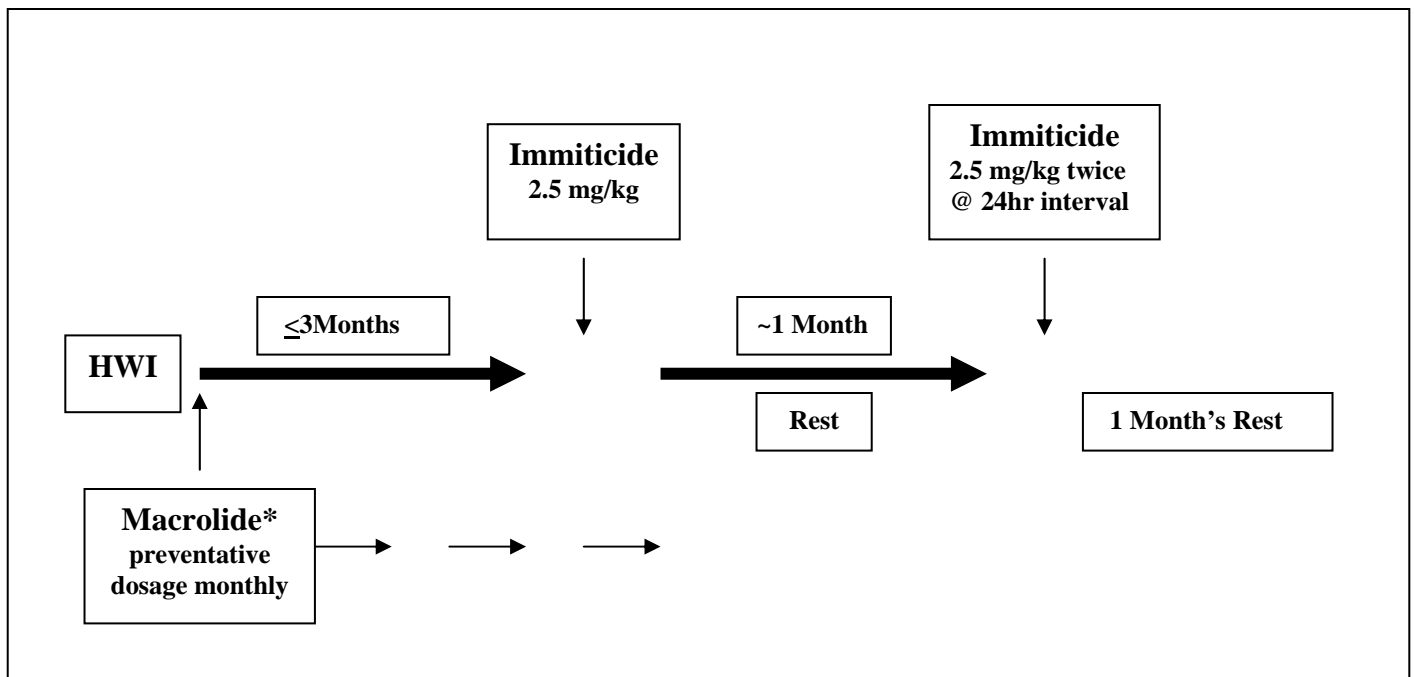
### PATIENT CLASSIFICATION and ADULTICIDE THERAPY in DOGS

Melarsomine dihydrochloride (IMMITICIDE<sup>®</sup>) emerged as a novel organic arsenical heartworm adulticide in the mid-nineties and is currently the only available drug approved for this purpose. It has inherent advantages over its predecessor, sodium caparsolate, being both safer and more efficacious. The drug is typically administered at

2.5 mg/kg IM twice, 24 hours apart, killing approximately 98% of immature and mature adult heartworms. Importantly, in more severe (Class 3; Table 2) heartworm disease (HWD), melarsomine may be administered in a “split dose”. With this approach, an initial injection is followed in **approximately** 1 month by a series of 2 injections over a 24 hour period, thereby lowering the initial kill rate and, hence, the impact of dying worms on the pulmonary vasculature.

<b>Table 2</b>			
<b>Class 1</b> <b>Heartworm Infection</b> <i>(asymptomatic, no radiographic lesions)</i>	<b>Class 2</b> <b>Symptomatic Heartworm Disease</b> <i>(mild to moderate signs)</i>	<b>Class 3</b> <b>Symptomatic Heartworm Disease</b> <i>(severe signs)</i>	<b>Class 4</b> <b>Caval syndrome</b>
2 doses melarsomine 24 hours apart (2.5 mg/kg IM)	2 doses melarsomine 24 hours apart (2.5 mg/kg IM)	1 dose melarsomine (2.5 mg/kg IM), followed in approximately 1 month with 2 injections 24 hours apart	Melarsomine not indicated for acute care

**Figure 1**



Despite the enhanced safety of this product, adverse reactions are still noted . In fact, successful pharmacological adulticidal therapy, by definition, dictates that thromboembolic events will occur. The severity of this complication can be diminished by severely restricting exercise after melarsomine administration and by using the “split dose” regimen recommended for Class 3 heartworm disease. The author recommends 1 month of severe exercise restriction after adulticidal therapy. The method and degree of exercise restriction varies with the client needs and the pet’s inherent activity level, but might include hospitalization, cage rest, sedation, housing in a restricted room of the house or garage and use of only gentle leash walks. Nevertheless, some owners do not or cannot restrict exercise, resulting in or worsening thromboembolic complications. Additionally, severe adverse reactions may be noted when dogs are incorrectly (or even correctly) categorized as Class 1 or Class 2 HWD severity and subsequently treated with the traditional 2-injection regimen. To minimize the chance of thromboembolic complication, the author has adapted an alternative approach, recommending the 3-injection (“split dose”) method in **all** Class 1, 2, or 3 heartworm infection.

## Method

At the time of diagnosis by a positive heartworm antigen test the author completes a minimum database, which includes a microfilariae test, chemistry panel, CBC, urinalysis, and thoracic radiographic evaluation. At this time, monthly macrolide preventative is prescribed (Figure 1). This approach is used to prevent further infection, to eliminate microfilariae (chronic therapy renders the dog of no further risk to infect itself or other dogs and cats), and to destroy developing L4, not yet susceptible to adulticidal therapy. In microfilaremic dogs, the first macrolide dosage is administered in the hospital or at home with observation so that an adverse reaction might be recognized and treated promptly. Corticosteroids with or without antihistamines (dexamethasone at 0.25 mg/kg IV and benadryl at 2 mg/kg IM OR 1 mg/kg of prednisolone PO 1 hour before +/- 6 hours after administration of the first dose of preventative) are commonly administered to reduce the potential for adverse reaction in highly microfilaremic patients. It is important to emphasize that adverse reactions are unusual with macrolides at preventative doses.

Depending on the time of year, up to 2-3 months *might* be allowed to lapse before adulticidal therapy is administered. Monthly macrolide administration ensures that the dog does not receive further infection. The delay allows for larval maturation to adulthood, ensuring that the only stage of the life cycle present is the adult, which is vulnerable to melarsomine therapy. This delay is particularly important if the diagnosis is made during or at the end of a mosquito exposure season. If the diagnosis is made in the spring or late winter, when infective larvae have matured, adulticidal therapy may be immediately administered (Figure 1).

The first injection of Melarsomine is administered by deep IM injection (2.5 mg/kg) in the lumbar musculature as described in the package insert and the injection site recorded. The injection needle is changed before injection and care is taken to inject deep into the muscle and nowhere else. It is important to remember that



the injection must be made into the center of the epaxial muscle (Figure 2). Patients are typically hospitalized for the day of the injections. The need for exercise restriction for 1 month is emphasized and sedation is provided, if necessary. Owners are also advised regarding potential adverse reactions (fever, lassitude, inappetence, cough, dyspnea, collapse) and to call if they have concerns. The owners are advised that they must return for a second series of 2 injections in **approximately** 1 month. Extending the time between the first injection and the subsequent two injections has no adverse effects on adulticide efficacy.

If serious systemic reaction results, the second stage of the adulticidal treatment is delayed or, occasionally, even cancelled. Typically, however, even with severe reactions, the entire treatment protocol is completed within 2-3 months (Figure 1). After a minimum of 1 month, the melarsomine injection procedure is repeated, again with recording of the injection site. If significant local reaction was noted after the first injection, dexamethasone or oral non-steroidal anti-inflammatory drugs to minimize pain at the injection site accompany subsequent injections. The following day (approximately, 24 hours after the first injection) the process is repeated with injection into the opposite lumbar area. Client instructions are similar to those previously given with reemphasis of the need for strict exercise restriction. Antigen testing is repeated 6 months following the second series of injections, with a positive test result indicating incomplete adulticidal efficacy. It is emphasized that, despite the proven efficacy of melarsomine, not all worms are killed in every patient. Worm burden is typically markedly reduced but if as few as 1-3 adult female worms remain, positive antigen tests are likely. Whether or not repeat adulticidal therapy is warranted, under these circumstances, is decided on a case by case basis with input from the owners.

## Justification

This “split dose” or 3-injection method enhances both the efficacy and safety of melarsomine adulticidal therapy. Studies have shown that patients treated with the split dose regimen have a higher seroconversion to a negative antigen status (89.7%) rate than patients treated with either caparsolate (65.9%) or the standard melarsomine dosing regimen (76.2%). Additionally, in a study using experimental heartworm infection in dogs, more effective adulticide activity did not appear to increase the severity of clinically apparent pulmonary hypertension or thromboembolism. Perhaps more importantly, killing worms in 2 increments of approximately 50% each diminish the insult to the lung and pulmonary vasculature. After approximately 50% of the worms are

destroyed, the lungs are allowed to heal for 1 month before the second insult. In addition, if there is a significant adverse reaction to the initial adulticidal injection, the 2<sup>nd</sup> and 3<sup>rd</sup> injections can be delayed (or even cancelled), until clinical signs have resolved and damaged tissue can heal – typically 2-3 months.

### **Drawbacks**

Disadvantages to this approach include added cost of the 3<sup>rd</sup> injection. This may well be counteracted by reduction in adverse reactions, which often require hospitalization and intensive therapy. Secondly, the total arsenical dosage is increased. We have found the approach to be generally well tolerated but would advocate a 2-dose regimen and fluid therapy in dogs with significant renal disease who require heartworm adulticidal therapy. Lastly, exercise restriction is often a problem for owners and the “split dose” regimen requires approximately 2 months’ exercise restriction (Figure 1). This may prove difficult or even impossible for some owners.

### **Conclusions**

The author believes that this 3-injection approach of melarsomine administration in the management of virtually *all* heartworm infections is safer and probably more effective than the 2-dose regimen, justifying the increased cost. Even if owners cannot afford the minimum database for evaluation of general health and the presence and severity of heartworm disease, they may still benefit financially by use of the 3-dose regimen. In such instances, even though the attending clinician has more difficulty predicting an adverse reaction without thoracic radiographs, he or she can reduce the likelihood of adverse reaction (and attendant costs) by the approach described here.

### **ANCILLARY THERAPY**

Corticosteroids are indicated in HWD in the face of pulmonary parenchymal complications (including PTE), to treat or prevent adverse reactions to microfilaricides, and possibly to minimize tissue reaction to melarsomine. Early studies demonstrated that corticosteroid therapy reduced pulmonary blood flow and worsened intimal disease in a model of HWI after adulticide. Subsequent studies however have suggested that corticosteroids actually decrease the severity of intimal disease and clinical signs of PTE. For allergic pneumonitis, prednisolone (1 mg/kg/day) is administered for 3-5 days and tapered as indicated.<sup>27</sup> The response is generally favorable. Prednisolone has also been advocated for the management of PTE. Because of the potential for fluid retention, steroids should be used cautiously in the face of heart failure.

Antithrombotic agents have received a good deal of attention in the management of HWD. Potential benefits include reduction in severity of vascular lesions of HWD, reduction in pulmonary arterial vasoconstriction and pulmonary hypertension, as well as minimization of post-adulticidal PTE. Aspirin has shown success in diminishing the vascular damage caused by segments of dead worms, reduced the extent and severity of myointimal proliferation caused by implanted living worms, and improved pulmonary parenchymal disease and intimal proliferation in dogs receiving thiacetarsamide after previous living HW implantation. More recent studies, however, have produced controversial results. Aspirin administered to dogs with implanted HW, receiving adulticide, showed no improvement in pulmonary angiographic lesions and had more severe vascular tortuosity than did controls and dogs receiving heparin. These authors emphasized that the ideal aspirin dosage would inhibit platelet function, but not PGI<sub>2</sub> production. Dillon and associates demonstrated that the aspirin dosage required to decrease platelet reactivity by at least 50% was increased by nearly 70% with HWI (implantation model) and by nearly 200% with a model (dead worm implantation) of PTE. There were not significant differences in severity of pulmonary vascular lesions in aspirin-treated vs control dogs. For these reasons, the American Heartworm Society does not endorse antithrombotic therapy for routine treatment of HWD.

Cage rest is an important aspect of the management of HWD after adulticidal therapy, after PTE, or during therapy of heart failure. This can often be best, or only, accomplished in the veterinary clinic. If financial constraints preclude this, crating at home and/or tranquilization are useful alternatives.

### **ADULTICIDE THERAPY IN CATS**

It is the author's opinion that asymptomatic cats with heartworm infection should **not** receive any form of adulticide therapy. The fact that most cats infected with *D. immitis* are asymptomatic and the lifespan of *D. immitis* in the cat is so short, argues against the necessity for adulticide therapy. However, the pulmonary pathology

associated with *D. immitis* infection and the possibility of acute death would seem to argue in favor of initiating adulticide therapy following definitive diagnosis. Although many published reports have stated that cats tolerate thiacetarsamide (Caparsolate®) therapy with minimal renal or hepatic toxicity these same reports are also quick to point out that cats seem to have severe thromboembolic complications. In an experimental study evaluating the pharmacokinetics of thiacetarsimide in normal cats, 3 of 14 cats developed an idiosyncratic acute respiratory distress syndrome resulting in pulmonary edema, respiratory failure and death within 1-3 hours of the second dose of thiacetarsamide. Subsequent investigations of a similar nature have been unable to reproduce this observation. Little data regarding the use of Immiticide™ in cats is available. An abstract reporting the use of Immiticide™ in cats with experimental (adult transplant) infection suggested that a single dose (2.5 mg/kg IM) reduced the worm burden by approximate 30% (statistically insignificant) without serious complications. Immiticide™ is not approved for use in cats.

Cats presented for cough and/or dyspnea may initially respond to administration of corticosteroids and bronchodilators. The initial prednisolone dose is 1 mg/kg orally twice daily for 10-14 days then the dose is gradually reduced to the minimum dose that will eliminate clinical signs. Theophylline (TheoDurJ) 25 mg/kg orally once daily in the evening for the duration of the infection. If clinical signs are not relieved by symptomatic therapy, then adulticide therapy can be considered but is not recommended. It is generally accepted that cats have more severe post-therapy thromboembolic complications than dogs probably due in part to the large size of the worms relative to the cats pulmonary artery. The clinician should expect a 30% patient mortality rate associated with adulticide therapy and subsequent thromboembolic complications. This high mortality rate may reflect the fact that cats which do not respond to symptomatic therapy may have more severe disease or higher worm burdens and are therefore at more risk for significant complications. Interestingly a retrospective report which tried to assess the outcome in treated (adulticide) versus non-treated (only supportive care given) reported no difference in longterm survival.

Supportive care for thromboembolic complications includes corticosteroid administration, oxygen supplementation, and cautious fluid therapy. The thromboembolic complications seem to be most severe approximately 5-14 days following adulticide therapy. Although the use of aspirin has been advocated in the treatment of feline dirofilariosis, experimental evidence suggests that even at near toxic doses, aspirin has little effect on the arteriographic, hemodynamic and histopathologic abnormalities. Aspirin administration as an adjunctive therapy in heartworm disease is no longer advocated by the AHS.

The dismal outcome associated with conventional therapy has prompted several investigators to pursue transthoracic and transvenous approaches for surgical removal of adult heartworms. Brown and colleagues have removed adult worms from 5 cats using either a left or right thoracotomy. Cats with worms located primarily in the right atrium and caeve undergo a right lateral thoracotomy and right atriotomy while cats in which worms are seen only in the pulmonary artery undergo a left lateral throcatomy and pulmonary arterotomy. Using either a 2.5 mm diameter 2-3 pronged bronchoscopic grasping device or standard 10 cm length alligator forceps Thomas and colleagues have successfully removed adult worms from 3 of 4 cats. The forceps were manipulated using standard left sided echocardiographic imaging planes to adjust positioning. Venco et al report similar results using a flexible alligator forcep As techniques are refined surgical removal of adult heartworms may become the therapy of choice for symptomatic adult infections. Acute respiratory and cardiovascular failure have been reported during surgical heartworm retrieval typically following a worm being crushed or fragmented. Pretreatment with corticosteroids and/or antihistimes may reduce the severity of these types of reactions.

## **MICROFILARICIDAL THERAPY**

Despite the fact that no available agent is FDA-approved for the elimination of microfilaria, microfilaricidal therapy is traditionally instituted 4-6 weeks after adulticide administration. Microfilaria are efficiently and rapidly cleared with ivermectin at 50 µg/kg (approximately 8 times the preventative dose) or with milbemycin at 500 µg/kg (the preventative dose), although each of these treatments represent extra-label uses of the drugs. Ivermectin can be diluted 1:9 in propylene glycol (Ivomec<sup>R</sup>, MSD Agvet, Rahway, NJ) or in water (Eqvalan<sup>R</sup>, MSD Agvet, Rahway, NJ) and administered orally at 1 ml/20 kg, although is practice is now strongly discouraged by the AHWS.

Adverse reactions, the severity of which is likely related to microfilarial numbers, were observed in 10% (6% severe and 4% mild) of 126 dogs receiving ivermectin at the microfilaricidal dose. Signs included shock, depression, hypothermia, and vomiting. With fluid and corticosteroid (dexamethasone at 2-4 mg/kg IV) therapy, all

dogs recovered within 12 hours. One fatality was observed 4 days after microfilaricidal therapy. Similar findings and frequency have been reported with milbemycin at the *preventative* dosage. Dogs so treated should be hospitalized and carefully observed for the day. Dogs <16 kg, harboring >10,000 microfilaria per ml blood are more apt to suffer adverse reactions. Benadryl (2 mg/kg IM) and dexamethasone (0.25 mg/kg IV) can be administered prophylactically to prevent adverse reactions to microfilaricidal doses of macrolides.

A 90% microfilaricidal success rate can be expected with high dose ivermectin. Milbemycin, at 500 µg/kg, cleared 6/8 (75%) dogs which had received adulticide therapy and did not harbor male and female adults; microfilarial numbers were reduced by 99% on the day after treatment. A slower microfilarial kill rate can also be achieved with ivermectin, moxidectin, and selamectin at preventative doses. Microfilaricide therapy is infrequently necessary in cats as greater than 80% of all cases are occult. Dithiazanine iodide can be used at a dose of 6-10 mg/kg daily orally for 7 days. Both ivermectin and milbemycin at the preventative dose are effective microfilaricides and should render cats microfilaria negative after 3-12 months of therapy.

This author chooses an alternative approach beginning the administration of a macrolide preventative at the time of diagnosis, often days to weeks prior to adulticide therapy. The advantage to this approach is that preventative is administered earlier. This allows immediate closure of the open theoretical window of HW exposure, while awaiting and 6 weeks beyond adulticide administration. With the "slow microfilaricides" (ivermectin, moxidectin, or selamectin), there is little chance of an adverse reaction, but the owner is warned and advised to administer the medication on a day when he/she will be at home. If milbemycin is used, it is administered in the hospital and/or preceded by administration of dexamethasone and benadryl, as described above.

## PREVENTION OF HEARTWORM INFECTION IN DOGS

The introduction of the macrolide agents ivermectin (Heartgard<sup>R</sup>), milbemycin oxime (Interceptor<sup>R</sup>), moxidectin (ProHeart<sup>R</sup> and ProHeart<sup>R</sup> 6) and selamectin (Revolution<sup>TM</sup>) has provided the veterinary profession with effective heartworm (HW) preventatives in a variety of formulations. Such agents, because they interrupt larval development during the first 2 months after infection, have a large window of efficacy and are administered monthly or less frequently. These agents are superior to diethylcarbamazine (DEC) in: convenience; producing less severe reactions when inadvertently given to microfilaremic dogs; allowing a grace period for inadvertent lapses in administration; efficacy with treatment lapses of up to 2-3 months when used continuously for the next 12 months; and lastly, having a dual role as microfilaricides.

Ivermectin, a chemical derivative of avermectin B<sub>1</sub> which is obtained from *Streptomyces sp.* is effective against a range of endo- and ectoparasites and is marketed as a once monthly heartworm preventative. It is marketed in a form with pyrantel pamoate to improve efficacy against intestinal parasites (Table 3). Macrolides offer a wide window of efficacy and provide some protection when treatment lapses (of up to two months) occur. This "reachback" effect is extended with continuous 12-month administration of ivermectin post-exposure to 3 months with 98% efficacy and to 4 months with 95% efficacy. As stated above, ivermectin is microfilaricidal at preventative doses (6-12 µg/kg/month), resulting in a gradual decline in microfilarial numbers. Despite this gradual microfilarial destruction, generally mild, adverse reactions (transient diarrhea) can occur if administered to microfilaremic dogs. Collies have been identified as a breed in which certain individuals are at increased risk of central nervous system signs and even death due to increased concentrations of ivermectin in the central nervous system. It is important to note that such adverse reactions have not been identified at preventative or even microfilaricidal doses of ivermectin. When used appropriately, ivermectin is virtually 100% effective in preventing HWI. Additionally, recent studies have shown ivermectin to have partial adulticidal properties when used continuously for 16-32 months.

Milbemycin oxime is a member of a family of milbemycin macrolide antibiotics derived from a species of *Streptomyces*. At 500-999 µg/kg, it has efficacy against developing filarial larvae, arresting development in the first 6 weeks. It can therefore be given at monthly intervals with a "reachback effect" of 2 months when doses are inadvertently delayed. With 12 months' continuous treatment post-exposure, this "safety net" can be extended to 3 months with 97% efficacy, falling to 41% with lapses of 4 months. At the preventative dosage, milbemycin is a broad-spectrum parasiticide, also demonstrating effectiveness against certain hookworms, roundworms, and whipworms. Milbemycin is also safe for use in collies when prescribed at the preventative dose. With appropriate use, milbemycin is virtually 100% efficacious as a HW prophylactic. In microfilaremic dogs, milbemycin has greater potential for adverse reactions than do other macrolides, as it is a potent microfilaricide at preventative doses.<sup>2</sup> Adverse reactions, similar to those observed with ivermectin at microfilaricidal doses (50 µg/kg) may be observed in microfilaremic dogs receiving preventative doses of milbemycin. Milbemycin has been used in an extra-label

manner to eliminate microfilaria. As for microfilaricidal dosages of ivermectin, pretreatment with Benadryl® (2 mg/kg IM) and dexamethasone (0.25 mg/kg IV), prior to milbemycin treatment, may prevent adverse reactions, particularly in dogs with high microfilarial counts.

Most recently, a semi-synthetic macrolide, selamectin, has been developed and marketed. It is unique in its spectrum and in the fact that is applied topically once monthly. Its efficacy is similar to that of other macrolides (virtually 100%, when used as directed). At 6-12 mg/kg topically, this preventative is effective at preventing heartworm infection and kills fleas and flea eggs, sarcoptic mange mites, ticks and ear mites. Bathing and swimming, as soon as 2 hours after application, did not affect efficacy. Safety has been shown at 10-fold topical doses, with oral consumption of single doses, and, in ivermectin-sensitive collies, at recommended dosages and five-fold overdoses for 3 months. Like other macrolides, selamectin has at least a 2 month "reachback effect" and with 12 months' continuous administration, is 99% protective after 3 month lapses in prophylaxis. Selamectin has microfilaricidal activity similar to other macrolides.

In summary, the macrolides offer a convenient, effective and safe method of HW prophylaxis with varying spectra and methods of administration (Table 3). Prophylaxis should be commenced at 6-8 weeks of age in endemic areas, or as soon thereafter as climatic conditions dictate. Although safer than DEC in microfilaremic dogs, before first time administration, any dog over 6 months of age and at risk of infection, should be tested (antigen test, followed by a microfilaria test, if positive). Although protective for at least 8 weeks post-exposure, macrolides should be administered precisely as indicated by the manufacturer. If accidental lapses occur, the preventative should be reinstated at recommended doses and maintained continuously for 12 months. If a lapse in preventative is prolonged (>2 months) and the risk for HWI deemed moderate or high, macrolides should be continued for a year without interruption. In addition, an antigen test should be performed approximately 6 months after the last chance for exposure to detect infection. Recent events have emphasized the importance of serial antigen testing when product switching is considered. If product switching is considered the author recommends obtaining a contemporary (at the time the switch is made), another test 4 months following the switch and then one at a year following the switch. This testing schedule will allow determination of the product involved in prevention failure if one were to occur.

### PREVENTION OF HEARTWORM INFECTION IN CATS

Heartworm (HW) prevention should be discussed with every cat owner and considered for all cats cared for by veterinarians and students in this hospital. The estimated risk of heartworm infection among the population of chronically unprotected cats is about 20% of that in unprotected dogs in an area. Many people consider the low risk of feline HW disease to be so low that prevention is not important. However, feline HW disease is especially severe, and there is no available treatment. In many cases, the first sign is the only sign: sudden death. Other cats develop spontaneous worm death with life-threatening pulmonary inflammation/non-cardiogenic edema. Since the disease is very easy to prevent, and the products are both safe and effective, at a minimum the potential value of HW prevention in cats should be reasonably discussed with our clients. Although it is most likely safe to administer preventative medications to the vast majority of cats (even HW positive cats), the authors recommends obtaining at least an Ab titer prior to dispensing any product. This helps establish the exposure status of the individual patient and over time will help determine the exposure status of your practice population.

- Drugs Used for Prevention of Feline HW Disease
- Heartgard® for cats brand of ivermectin  
oral tablet given once monthly (Merial)
  - Interceptor® for cats brand of milbemycin oxime  
oral tablet given once monthly (Novartis)
  - Revolution® brand of selamectin  
topical treatment applied monthly (Pfizer)

**Table 3. Comparison clinical spectrum of commercially available macrolides**

Drug	HW	Mf	Adulticidal	Hook	Whip	Round	Tape	Flea/eggs	Tick	Sarcoptes	Ear Mites	
Ivermectin	+	+	+	+*		+*						Ch

<b>Milbemycin</b>	+	++		+	+	+		-/+**				Tab
<b>Selamectin</b>	+	+	(+)					+/+	+	+	+	Top

() = partially effective or incompletely studied. Ch = chewable, Tab = flavored tablet, T/I = tablet or injectable, Top = topical. \*ivermectin/pyrantel pamoate, \*\*milbemycin/lufenuron, \*\*\*injectable formulation