# CANINE HEARTWORM DISEASE

Canine - Guidelines for the Diagnosis, Prevention and Management of Heartworm (*Dirofilaria immitis*) Infection in Dogs

Feline - Guidelines for the Diagnosis, Treatment and Prevention of Heartworm (*Dirofilaria immitis*) Infection in Cats

**Contents**

## 2005 Guidelines for the Diagnosis, Prevention and Management of Heartworm (*Dirofilaria immitis*) Infection in Dogs

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**Preamble**

These recommendations are based on the latest information presented at the 2004 triennial symposium of the American Heartworm Society. Revisions to the last recommendations, published in 2003, are based on new research and additional clinical experience, particularly in the areas of heartworm chemoprophylaxis, and serologic testing/retesting. This document focuses primarily on procedures and largely omits discussion of the better known pathophysiologic mechanisms and clinical features of heartworm disease in dogs. Guidelines for the diagnosis, treatment and prevention of heartworm infection in cats are contained in a separate document.

**EPIDEMIOLOGY**

**Heartworm infection in dogs has been diagnosed around the globe, including all**

50 of the United States. In the U.S., its territories and protectorates, heartworms are considered at least regionally endemic in each of the contiguous 48 states, Hawaii, Puerto Rico, U.S. Virgin Islands and Guam. Heartworm transmission has not been documented in Alaska and even with the importation of microfilaremic dogs, it is doubtful the climate this far north will permit maturation of infective larvae. Relocation of infected, microfilaremic dogs appears to be the most important factor contributing to further dissemination of the parasite. The ubiquitous presence of one or more species of vector competent mosquitoes makes transmission possible wherever a reservoir of infection and favorable climatic conditions co-exist.

A climate that provides adequate temperature and humidity to support a viable mosquito population, and also sustain sufficient heat to allow maturation of ingested microfilariae to infective, third-stage larvae (L3) within this intermediate host is a pivotal prerequisite for heartworm transmission to occur. Laboratory studies indicate that development and maturation requires the equivalent of a steady 24-hour daily temperature in excess of 64°F (18°C) for approximately one month. Intermittent diurnal declines in temperature below the developmental threshold of 57°F (14°C) for only a few hours retard maturation, even when the average daily temperature supports continued development. At 80° F (27° C), 10 to 14 days are required for development of microfilariae to the infective stage.

The length of the heartworm transmission season in the temperate latitudes is critically dependent on the accumulation of sufficient heat to incubate larvae to the infective stage in the mosquito. The peak months for heartworm transmission in the Northern Hemisphere are July and August. Algorithmic predictions based on analysis of historical temperature records have consistently overestimated actual transmission periods confirmed independently by a variety of field studies and appear to represent conservative guidelines. Under the most favorable conditions, these estimates range from less than four months in southern Canada to potentially all year in the subtropical zones of southern Florida and the Gulf Coast. The model predicts that heartworm transmission in the continental U.S. is limited to six months or less above the 37th parallel, i.e., Virginia-North Carolina State line.

Where the prevalence is low, a nidus of heartworm infection may be detected which usually represents both a focal spread of infection and heightened awareness through increased testing. Once a reservoir of microfilaremic domestic and wild canids is established beyond the reach of veterinary care, eradication becomes improbable.

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### PRIMARY DIAGNOSTIC SCREENING

**Test Timing for Optimal Results**

The earliest that heartworm antigen and microfilariae can be detected is about five and 6.5 months post-infection, respectively. Depending on the sensitivity of the particular heartworm antigen test, antigenemia may precede, but sometimes lags the appearance of microfilariae by a few weeks. In low worm burdens or with animals on macrocyclic lactones chemoprophylaxis, antigenemia may be delayed to approximately nine months post infection. The interval of time between infection and the expected first appearance of microfilariae is the prepatent period. To determine when testing might become useful, a predetection period should be added to the approximate date on which infection may have been possible. A reasonable interval is seven months. Thus, there is generally no need or justification for testing a dog for antigen or microfilariae prior to about seven months of age. To detect an infection occurring any time during the preceding

transmission season, the predetection period should be added to the approximate end of that period. Indiscriminate testing at any time of the year in an effort to distribute the workload may put the date of testing within the predetection period and waste the test, as far as determining if infection occurred the preceding season. Puppies born during periods when no heartworm transmission is occurring do not need to be tested before starting chemoprophylaxis the following spring. In the cooler regions, transmission may cease in time to allow infections occurring late in the season to mature before transmission resumes. If so, testing late in the spring is likely to detect infections from the preceding year. However, where transmission continues late into the year, the predetection period may overlap the beginning of the next season. If so, monthly chemoprophylaxis should commence (or continue if never interrupted) within 30 days following the start of the new season. If the possibility of an infection occurring late in the preceding season is a concern, testing should be delayed until such time when a positive result is possible.

When changing chemoprophylaxis products, special consideration needs to be taken for assessing heartworm status. Dogs should be tested immediately prior to changing and approximately four months after initiation of the new chemoprophylaxis to evaluate the efficacy of the original product (see RETESTING). Testing at four months is most appropriate to detect prior product efficacy failures. If testing at five months or later after changing products, there is a risk that there will be equivocal results as to which product has been ineffective.

Microfilaria vs. Antigen Testing

Whether screening a population of asymptomatic dogs or seeking verification of a suspected heartworm infection, antigen testing is the most sensitive diagnostic method. Microfilaria testing is complementary and may be done in tandem with antigen testing to specifically determine whether this life-cycle stage is also present in dogs that are antigenemic. Even in areas where the prevalence of heartworm infection is high, many (~20%) heartworm-infected dogs may not be microfilaremic. The current generation of heartworm antigen tests identify most "occult" (microfilaria negative) infections consisting of at least one mature female worm and are nearly 100% specific. Since less than 1% of infections are patent but not antigenemic, testing for antigen will detect more infections than testing only for microfilariae.

Antigen Tests

ELISA and immunochromatographic test systems are available for detecting circulating heartworm antigen. Each testing format has proved to be clinically useful. Differences in sensitivity exist but these are statistically insignificant. False negative results also can occur erratically with any one test, which is why unexpected negative results can sometimes be reconciled by retesting with a different test. Specificity is consistently very high with all the antigen tests, and this is their most important attribute. Selection of a test kit should not be based solely on claims of comparative sensitivity, but also should consider practice preference for "batching" multiple (but separate) samples or individual, "in-room" sample testing, technician capabilities, technical support, critical timing for reading results, clarity of end result, and unit cost.

The amount of antigen in circulation bears a direct but imprecise relationship to the number of mature female heartworms. A graded test reaction can be recognized by ELISA test systems but quantitative results are not displayed by immunochromatographic tests. The utility of the ELISA tests for assessing the degree of parasitism is limited by such confounding complications such as the transient increase in antigenemia associated with recent worm death. Therefore, quantitative analysis of antigen results is highly speculative and requires correlation with other relevant information. For example, radiographic evidence of advanced pulmonary arterial disease typical of chronic heartworm disease and a

low or absent antigenemia is consistent with the aftermath of a previous infection that has been cleared, either naturally or by treatment.

To obtain reliable and reproducible results, antigen tests must be performed in strict compliance with the manufacturer's instructions. This has been simplified for several tests that use devices that minimize the number of steps and partially automate the procedure. False positive results can occur but usually are due to technical error, such as inadequate washing steps or delay in reading the test. If the validity of a weakly positive result is in doubt, verification may be achieved by repeating the test and if still ambiguous, independent confirmation by some other means, such as a second antigen test format, concentration tests for microfilariae, thoracic radiography to detect signs of heartworm disease or ultrasonographic visualization of worms. Also upon request, most test manufacturers will analyze ambiguous samples in their own laboratories. If there has not been much potential for exposure, it is recommended to confirm all positive antigen tests in asymptomatic dogs prior to any adulticide therapy.

False-negative test results occur most commonly when infections are light, female worms are still immature, only male worms are present and/or the test kit (for test kits requiring refrigeration) or sample has not been warmed to room temperature. Antigen test results should be interpreted carefully, taking other relevant clinical information into consideration. However, in general, it is better to trust rather than reject antigen test results, unless that interpretation is contradicted strongly by independent clinical evidence or circumstances influencing the probability of infection.

Microfilaria Tests

Most microfilaremic dogs can be detected by microscopically examining fresh blood for cell movement created by the motility of the microfilariae. A stationary rather than a migratory pattern of movement is indicative of a dirofilaria species, nearly always *D. immitis* in the U.S. Movement beneath the buffy coat in a microhematocrit tube also may be visible microscopically. However, these are insensitive methods for examining blood in which low numbers (50-100/ml) of microfilariae are present. Therefore, it should not be assumed that no microfilariae are present until at least 1.0 ml of blood has been examined using a concentration technique (modified Knott test or filtration test). The modified Knott test is the preferred method for observing morphology and measuring body dimensions to differentiate *D. immitis* from non-pathogenic filarial species such as *Acanthocheilonema* (formerly *Dipetalonema*) *reconditum*. Although screening may be based entirely on antigen testing, antigen-positive dogs should also be tested for microfilariae, because a microfilaremia validates the serologic results and identifies the patient as a reservoir of infection.

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HEARTWORM CHEMOPROPHYLAXIS

Canine heartworm infection is preventable, despite the inherent susceptibility of dogs. Since most dogs living in heartworm endemic areas are at risk, chemoprophylaxis is a priority. Puppies should be started on chemoprophylaxis no later than 8 weeks of age. Evidence strongly suggests that by reducing the reservoir population through increasing the number of dogs receiving chemoprophylaxis, a disproportionately large decrease in the prevalence of infection among unprotected dogs may occur relative to the percentage of additional dogs receiving chemoprophylaxis. This collateral protection spreads the umbrella of chemoprophylaxis most effectively in communities where heartworm prevalence and dog population density are both relatively low.

With the exception of the subtropical south, heartworm transmission has distinct seasonal parameters (see Epidemiology). Therefore, regional climate should be taken into consideration when evaluating the potential for heartworm transmission. Since there are times of the year when lapses in chemoprophylaxis entail considerable risk, the vulnerable period should be emphasized objectively to sensitize owners to be particularly conscientious about treating their dogs when it is most important to do so.

Continuous, year-round, chemoprophylaxis may not be necessary throughout the northern half of the country in which the prospects for transmission are limited to the months of May through October, but it is important to note that successful seasonal prophylaxis depends on proper timing of heartworm preventative administration. In regions where heartworm transmission occurs more than half the year, seasonal chemoprophylaxis may not be the most effective method of chemoprophylaxis and year around treatment may be considered to enhance compliance which is known to be a serious problem throughout the country. Veterinarians may find that when using chemoprophylaxis products with endoparasite activity extending the period of administration enhances compliance and may assist in preventing zoonotic parasitic infections.

Options for effective chemoprophylaxis include several drugs administered either in oral, topical or parenteral formulations on a daily, monthly or six-month interval. Before starting a prophylactic regime, all mature dogs that may have been infected at least seven months earlier should be antigen tested, and in appropriate instances, also tested for microfilariae (see PRIMARY DIAGNOSTIC SCREENING). It is strategically important to determine heartworm status before starting chemoprophylaxis for the first time. This will avoid unnecessary delay in detecting subclinical infections and potential confusion concerning effectiveness of the prevention program, if a pre-existing infection becomes evident after beginning chemoprophylaxis (e.g. chemoprophylaxis initiated during the pre-patent period).

Heartworm chemoprophylaxis requires authorization by a licensed veterinarian having a valid relationship with the client and patient. To establish this relationship, heartworm prevention should be discussed with the client and if a record of past treatment does not exist, it may be necessary to test the patient before dispensing or prescribing chemoprophylaxis.

Macrocyclic lactones

The most commonly used heartworm chemoprophylactics are the macrocyclic lactones (ivermectin, milbemycin oxime, moxidectin and selamectin). These drugs have exceptionally high therapeutic/toxic ratios, and possess anthelmintic activity against microfilariae, 3rd and 4th stage larvae, and in some instances young adult heartworms. The filaricidal effect of oral and topical formulations on precardiac larvae is achieved by brief pulsing at very low doses, which makes these drugs virtually 100% effective at the prescribed doses and intervals of administration, and among the safest used in veterinary medicine.

The single dose retroactive efficacy of all these macrocyclic lactones is assured for one month, and remains high for at least an additional month. However, efficacy against older larvae declines and requires progressively longer-term administration as the worms age to achieve a high level of protection. The extended post-infection efficacy of the macrocyclic lactones is a safeguard in the event of inadvertent delay or omission of regularly scheduled doses and does not justify lengthening the recommended one month interval of administration for the oral and topical formulations.

The extent of retroactive efficacy has important implications for chemoprophylaxis in dogs that have either missed several doses during the transmission season, or are already well into the transmission season before chemoprophylaxis is started and may already be infected. Short lapses in administration can be accommodated. However, when omissions exceed ten weeks during the

transmission period, continuing monthly prophylaxis through the off-season in cooler climates has merit, since substantial protection still may be provided. This precautionary practice is acceptable even when the integrity of a seasonal prophylaxis program appears to remain intact, as some compliant owners' dogs become infected and year-round chemoprophylaxis will provide some safety-net (retroactive) coverage for these dogs, even when the owners and veterinarians are not aware the dogs are infected. When chemoprophylaxis is extended to compensate for interruptions, antigen testing should be performed after the predetection period has passed (see Test Timing for Optimal Results).

Testing prior to first starting chemoprophylaxis is advocated for the reasons stated previously. The macrocyclic lactones may be administered to heartworm-infected dogs with few or no microfilariae. However, dogs with moderate to high microfilarial levels should be carefully monitored following administration of these drugs, as they are the most effective microfilaricides available (see ELIMINATION OF MICROFILARIAE).

It is well known that some Collie dogs (autosomal recessive inheritance) and other p glycoprotein deficient dogs are unusually sensitive to high doses of ivermectin (in excess of 16 times the minimum effective prophylactic dose) but toxicosis has been reported with overdosage of other macrocyclic lactones as well. Often, these instances have occurred when concentrated livestock preparations of these drugs have been ingested. Dose miscalculation with extra-label use makes livestock formulations hazardous for dogs.

<u>Oral administration</u>: Ivermectin, milbemycin oxime and moxidectin are available for monthly oral administration. Some of these formulations are flavored and chewable to increase patient acceptance and facilitate administration. Dose units are packaged for dogs within prescribed weight ranges. To be maximally effective, administration should begin within one month of the anticipated start of transmission and the last dose should be given within one month after transmission ceases.

<u>Topical administration</u>: Selamectin is available as a topically applied liquid. The parameters for treatment with selamectin are the same as for monthly oral chemoprophylaxis.

The FDA has approved a topical formulation of ivermectin combined with imidacloprid.

<u>Parenteral administration</u>: A slow release (SR) formulation of subcutaneously injected moxidectin-impregnated, lipid microspheres provides single dose continuous protection in excess of six months. Moxidectin SR should be administered within one month of exposure to infective mosquitoes but is still more than 80% effective four months post-infection. Although information about the duration of back-end (>6 months post-treatment) efficacy is not presently in the public domain, full protection extends beyond six months. In areas where the risk of infection is limited to five to six months, a properly timed injection of moxidectin SR provides a comfortable margin of protection.

Moxidectin SR was voluntarily removed from the US market in September 2004 for issues related to safety. The manufacturer is still in negotiations with the US Food and Drug Administration to return the product to the US market. The product has not been withdrawn from the market in other countries.

Diethylcarbamazine Citrate (DEC)

Although protective, the efficacy of DEC is critically dependent upon uninterrupted daily administration during the prescribed period of use. Discontinuation for only two to three days may void protection temporarily. Consequently, compliance with the administration regime is even more important with DEC than with the macrocyclic lactones. Due to the lack of any appreciable retroactive effect from

DEC, administration must begin shortly before the anticipated start of the transmission season to ensure protection. Furthermore, since DEC is not immediately larvicidal, it is necessary to continue daily administration for two additional months after exposure to infective mosquitoes has ceased.

Testing for microfilariae is mandatory before initiating or restarting prophylaxis with DEC. Non dose-dependent gastrointestinal distress frequently develops shortly after administering DEC to previously untreated microfilaremic dogs. These reactions recur with each dose, and although usually self-limiting, may progress to hypovolemic shock and death. In dogs with occult infections, DEC may be started prior to adulticide therapy to prevent further infection. Dogs with an uncertain infection status, but having no microfilaremia, may be started on DEC. If a microfilaremia develops after DEC administration has begun, daily treatment may continue. However, if later interrupted or discontinued, DEC administration should not be resumed, since these dogs can develop the reactions typical of those that have never been exposed to the drug. Chemoprophylaxis should be switched to one of the macrocyclic lactones. Adulticide and subsequent microfilaricide treatments must be completed before resuming DEC administration.

After a lapse in DEC administration during the heartworm transmission season, a macrocyclic lactone should be started promptly for its retroactive chemoprophylactic effect. One dose should be sufficient to restore protection if the interruption was less than two months. If DEC administration is to be resumed, it should be restarted at the same time the bridging macrocyclic lactone dose is administered. When DEC is omitted for three months or longer, macrocyclic lactone administration (ivermectin or selamectin monthly or moxidectin SR every six months) should be extended for full-year coverage, as a precaution against latent infections.

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### RETESTING

As lack of effectiveness has been reported for all macrocyclic lactones, annual retesting is an integral part of ensuring that prophylaxis is achieved and maintained. Where heartworm transmission has a local seasonal cycle, scheduling for retesting should take into consideration the seven-month predetection period used for primary screening.

**Evaluation of Product Efficacy Following Noncompliance and Changing Products**

Evaluation of the efficacy of a heartworm preventive product administered to unprotected dogs over six months of age or to dogs in which there is a known or suspected breach in dosing compliance for three months or longer should be done with caution. Such a dog should be tested for antigen prior to starting (or resuming) preventive therapy and if antigen-negative, should be tested again four and nine months later. Considering that an antigen test may be positive as early as five months after infection and most dogs are positive by nine months (and assuming that noncompliance during the nine-month period was not an issue), a positive test result before dosing is started (or resumed) and/or at four months indicates that the dog was infected prior to initiation of dosing. If the dog is positive only at nine months, it is equally possible that the dog was infected prior to the first dose or that the product failed. If the dog is positive only after nine months, product failure is most likely the reason for infection.

When changing chemoprophylaxis products and noncompliance is not an issue, special consideration needs to be taken for assessing heartworm infection status and evaluating efficacy of the products. To most effectively evaluate the efficacy

of the original and new products, the dog should be tested for antigen prior to changing products, three months (for monthly products and DEC) or four months (6-month-injectable products) after changing products and again five months later (i.e., eight to nine months after changing products). If the dog is positive prior to changing products and/or at three to four months, the original product was ineffective. A positive test only at eight to nine months after changing products could be due to failure of either the original or the new product. Thereafter, a positive test result is most likely due to lack of full efficacy of the new product, if all previous tests were negative.

Practical considerations will probably result in testing at the time of the late start/resumption of chemoprophylaxis in a non-compliant case or product change in a compliant case, six months later (which gives only equivocal results as to which product has been ineffective) and then at the next annual examination. However, for medicalegal reasons and for manufacturer efficacy guarantees, additional testing at three to four months and eight to nine months, rather than at six months, is strongly recommended.

## Summary of Retesting Results

| Original Product | Test at change | Test timing after change (months) | Positive results | Confirmatory testing (months) | Positive results | Subsequent testing (months) | Positive results (if earlier negative) |
|---|---|---|---|---|---|---|---|
| DEC | Yes | 3 | Failure of original | 8 | Failure of either | >8 | Failure of new |
| Macrocyclic lactone (oral or topical) | Yes | 3 | Failure of original | 8 | Failure of either | >8 | Failure of new |
| Moxidectin SR | Yes | 4 | Failure of original | 9 | Failure of either | >9 | Failure of new |
| Unprotected dog or non-compliance >3 months | At (re-) initiation | 4 | Infected prior to initiation | 9 | Infected prior or failure of original | >9 | Failure of new |

## Monthly Ivermectin, Milbemycin Oxime, Moxidectin and Selamectin

Macrocyclic lactone chemoprophylaxis will clear microfilariae from the blood of dogs with patent infections by exerting a direct or indirect microfilaricidal effect, depending on the specific product used, and retarding repopulation by gradually suppressing embryogenesis. With uninterrupted dosing, elimination of microfilariae is usually complete within six to 12 months of oral dosing with monthly macrocyclic lactones or one month following moxidectin SR injection. Once the adults are sterilized, clearance is generally permanent unless the dog is re-infected. In the event a pre-existing prepatent infection matures after starting macrocyclic lactone chemoprophylaxis, microfilariae are unlikely to be found, or appear only transiently in small numbers. Since macrocyclic lactone chemoprophylaxis may negate microfilaria testing and microfilariae do not contribute to heartworm antigenemia, antigen testing is the most reliable method of retesting.

To verify that a chemoprophylaxis program has been successfully started, retesting approximately seven months following the end of the first transmission season is advised. A negative antigen test at this time generally ensures that a prepatent infection did not precede initiation of chemoprophylaxis, and that an adequate dose was administered to dogs started on chemoprophylaxis before attaining their mature weight.

Annual retesting will not fulfill the objective of early detection if performed indiscriminately within the calendar year without regard for the seven-month predetection period (see Test Timing for Optimal Results). For example, testing in early January will not detect an infection occurring in late July. If the next annual

retest is performed the following January, the effective testing interval is 18 months.

## Moxidectin SR Injections

Since administration of this form of chemoprophylaxis is completely under the control of a veterinarian, the medical record should leave no doubt about the timing and frequency of treatment. A retest should be performed after completion of the first cycle of protection to ensure that a prepatent infection was not present. As with all chemoprophylaxis products, periodic testing will ensure there have been no efficacy breaks

## Daily DEC

The chance is greater that brief interruptions in DEC administration will cause breaks in heartworm protection. In the event a microfilaremia should occur, these dogs are at serious risk of developing potentially fatal reactions following resumption of DEC chemoprophylaxis. Since antigen testing may miss an occasional microfilaremic dog, a microfilaria test must be run before resuming seasonal prophylaxis with this drug. Even if DEC is given daily throughout the year without interruption, it is still prudent to retest annually for microfilariae. Antigen testing is recommended highly for its greater sensitivity but is not a substitute for microfilaria testing when DEC is used for chemoprophylaxis.

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## OTHER DIAGNOSTIC AIDS

Additional testing methods are useful for confirming the diagnosis and staging the severity of heartworm disease.

## Radiography

Radiography provides the most objective method of assessing the severity of heartworm cardiopulmonary disease. Typical (nearly pathognomonic) signs of heartworm vascular disease are enlarged, tortuous and often truncated peripheral intralobar and interlobar branches of the pulmonary arteries, particularly in the diaphragmatic lobes. These findings are accompanied by variable degrees of pulmonary parenchymal disease. The earliest and most subtle pulmonary arterial changes are found in the dorsal caudal wedge of the diaphragmatic lung lobes. As the severity of infection and chronicity of disease progress, the pulmonary arterial signs are seen in successively larger branches, and in the worst cases, eventually the right heart also enlarges.

## Echocardiography

The body wall of adult heartworms is highly echogenic and produces distinctive, short parallel-sided images with the appearance of "equal signs" where the imaging plane cuts across loops of the parasite. Echocardiography can provide definitive evidence of heartworm infection, as well as allow for assessment of cardiac anatomic and functional consequences of the disease. However, it is not an efficient method of making this diagnosis, particularly in lightly infected dogs, since the worms often are limited to the peripheral branches of the pulmonary arteries beyond the echographic field of view. When heartworms are numerous, they are more likely to be present in the main pulmonary artery, right and proximal left interlobar branches, or within the right side of the heart where they can be imaged easily. In dogs with hemoglobinuria, visualization of heartworms in the orifice of the tricuspid valve provides conclusive confirmation of the caval syndrome.

## PREADULTICIDE EVALUATION

The extent of the preadulticide evaluation will vary depending on the clinical status of the patient and the likelihood of co-existing diseases that may affect the outcome of treatment. Clinical laboratory data should be collected selectively to complement information obtained from a thorough history, physical examination, antigen test and usually thoracic radiography.

The two most important variables influencing the probability of post-adulticide thromboembolic complications and the outcome of treatment are the extent of concurrent pulmonary vascular disease and the severity of infection. Assessment of cardiopulmonary status is indispensable for evaluating a patient's prognosis. Post-adulticide pulmonary thromboembolic complications are most likely to occur in heavily infected dogs already exhibiting clinical and radiographic signs of severe pulmonary arterial vascular obstruction, especially if congestive heart failure is present.

Although a very crude method of assessing the severity of infection, the strength of ELISA-based antigen test reactions may provide an indication of whether an infection is light or heavy (see Antigen Tests). Since radiographic signs of advanced pulmonary vascular disease may persist long after an infection has run its course, some of the most severely diseased dogs may have disproportionately low levels of circulating antigen by the time they are tested. Also some inactive dogs can have large worm burdens and be clinically asymptomatic with minimal radiographic changes.

## ADULTICIDE THERAPY

**Melarsomine Dihydrochloride**

Melarsomine is administered via deep intramuscular injection into the epaxial lumbar muscles. Mild swelling and some soreness at the injection site may be present for a few days, but this can be minimized by ensuring that the injection is deposited deeply with a needle of appropriate length and gauge for the size of dog and body condition. Strictly adhering to the manufacturer's instructions will minimize local reactions. Also, if adulticide treatment is elected for clinically ill dogs, an attempt should be made to stabilize the patient's clinical signs with medical support before proceeding with treatment. Exercise restriction during the recovery period is essential for minimizing cardiopulmonary complications (see Pulmonary Thromboembolism).

Adhering to the manufacturer's instructions and classifying the stage of disease will reduce the risk of pulmonary thromboembolism. The administration protocol of two injections separated by a 24-hour interval (= standard protocol) is recommended by the manufacturer for dogs at low risk of thromboembolic complications. For dogs at greater risk, a gradual, two-stage elimination of worms is possible using a three-injection treatment protocol of one dose initially, followed in four to six weeks with a two-dose treatment (= alternative protocol). By initially killing fewer worms and completing the treatment in two stages, the cumulative impact of worm emboli on severely diseased pulmonary arteries and lungs can be reduced.

The three-injection alternative protocol is the treatment of choice of the American Heartworm Society and several university teaching hospitals, regardless of stage of disease, due to the increased safety and efficacy benefits and subsequently fewer dogs that require further treatment with melarsomine.

Administration of a chemoprophylactic dose of a macrocyclic lactone should begin as soon as the dog is diagnosed with a heartworm infection. While controversial due to the theoretical risk of inducing resistance to macrocyclic lactones, it may be beneficial to administer a macrocyclic lactone for up to six months prior to administration of melarsomine, when the clinical presentation does not demand immediate intervention. The reasoning for this approach is to reduce circulating microfilariae and kill migrating *D. immitis* larvae, and in the case of ivermectin, stunt immature D. *immitis* and reduce female worm mass by inhibiting the reproductive system. Milbemycin also sterilizes female worms, but it does not affect worms older than four months. Administration for greater than three months should result in reduced antigenic mass, which in turn may reduce the risk of pulmonary thromboembolism. Depending on the season and geographic locale, administration for three months also will allow immature worms to reach an age at which they are known to be susceptible to killing by melarsomine[1].

[1] All macrocyclic lactones have a "reach back" of two months. As melarsomine has not been demonstrated to kill worms under four months of age, three doses of a macrocyclic lactone (or an injection of Moxidectin SR) will kill most pre-cardiac larvae and allow immature worms to reach the age that they will be susceptible to melarsomine.

Exercise restriction should be enforced from the time of diagnosis through the period of treatment. Milbemycin and parenteral moxidectin may cause a rapid decrease in microfilariae numbers and should be used with caution.

Antigen testing should be conducted six months post-treatment as part of the adulticide protocol (see Confirmation of Adulticide Efficacy).

Ivermectin Continuous monthly administration of prophylactic doses of ivermectin, alone or in combination with pyrantel pamoate, is highly effective against late precardiac larvae and young (<7 month post-infection) adult heartworms. Comparable adulticide capability of the other macrocyclic lactones has not been reported. The adulticide effect of ivermectin generally requires more than a year of continuous monthly administrations and may take more than two years before heartworms are eliminated completely. The older the worms when first exposed to ivermectin, the slower they are to die. In the meantime, the infection persists and continues to cause disease. Therefore, long-term continuous administration of ivermectin generally is not a substitute for conventional arsenical adulticide treatment. If arsenical therapy is declined, a lengthy course of prophylactic doses of ivermectin will gradually reduce the number of adult heartworms, but in chronic mature infections this may not be clinically beneficial. Exercise should be restricted in dogs treated with prophylactic doses of ivermectin as the adulticide.

The results of a recent study in which monthly ivermectin was administered to client-owned heartworm infected dogs for two years indicated that this method of killing adult heartworms should not be used in dogs with signs of heartworm disease or very active dogs, and if used in asymptomatic dogs, the dogs should be examined by a veterinarian at least once every four to six months until all of the worms are dead. As worsening of radiographic signs may be observed, periodic radiographic evaluations may be useful in monitoring the treatment.

Pulmonary Thromboembolism

Pulmonary thromboembolism is an inevitable consequence of successful adulticide therapy and may be severe if infection is heavy and pulmonary arterial disease is extensive. If signs of embolism (low grade fever, cough, hemoptysis,

exacerbation of right heart failure) develop, they are usually evident within 7 to 10 days but occasionally as late as four weeks, after completion of adulticide administration. Mild embolism in relatively healthy areas of lung may be inapparent clinically. A pivotal factor in reducing the risk of thromboembolic complications is exercise restriction during the critical month following treatment. Administration of diminishing anti-inflammatory doses of glucocorticosteroids may help control clinical signs of pulmonary thromboembolism, but studies to evaluate the effects of glucocorticoids on the efficacy of melarsomine have not been reported.

The empirical use of aspirin for its antithrombotic effect or to reduce pulmonary arteritis is not recommended for heartworm-infected dogs. Convincing evidence of clinical benefit is lacking, and there is some research suggesting that aspirin may be contraindicated.

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## SURGICAL EXTRACTION OF ADULT HEARTWORMS

**Caval Syndrome (Dirofilarial Hemoglobinuria)**

Caval syndrome develops acutely in some heavily infected dogs when large numbers of adult heartworms partially obstruct blood flow through the tricuspid valve and also interfere with valve closure. Severe passive congestion of the liver, a coarse systolic murmur of tricuspid regurgitation and jugular pulsations are characteristic features of the syndrome. The diagnosis is based on a sudden onset of severe lethargy and weakness accompanied by hemoglobinemia and hemoglobinuria. Caval syndrome can be confirmed conclusively by echocardiographic visualization of heartworms within the tricuspid orifice. The clinical course usually ends fatally within days if surgical extraction of the worms is not pursued promptly.

Surgical removal of worms from the right atrium and orifice of the tricuspid valve can be accomplished using local anesthesia and either a rigid or flexible alligator forceps or an intravascular retrieval snare introduced preferentially via the right external jugular vein. With fluoroscopic guidance if available, the instrument should continue to be passed until worms can no longer be retrieved. Immediately following a successful operation, the murmur should soften or disappear, and within 12 - 24 hours hemoglobinuria should disappear. Fluid therapy may be necessary in critically ill, hypovolemic dogs to restore hemodynamic and renal function. Within a few weeks following recovery from surgery, adulticide chemotherapy is recommended to eliminate any remaining worms, particularly if many are still visible echocardiographically.

**Pulmonary Arterial Infections**

The main pulmonary artery and lobar branches can be accessed with flexible alligator forceps, aided by fluoroscopic guidance. Intraoperative mortality with this technique is very low. Overall survival and rate of recovery by dogs at high risk of pulmonary thromboembolism is improved significantly by physically removing as many worms as possible before beginning adulticide therapy. When the facilities are available, worm extraction is the procedure of choice for the most heavily infected and high risk dogs. However, before electing this method of treatment, echocardiographic visualization of the right heart and pulmonary arteries should be performed to determine that a sufficient number of worms are in accessible locations.

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### ADDITIONAL CONSIDERATIONS FOR ADULTICIDE THERAPY

*Wolbachia*

Most filarial nematodes, including *D. immitis*, harbor obligate, intracellular, gram-negative bacteria belonging to the genus *Wolbachia* (*Rickettsiales*). In infections with other filarial parasites, treatment with tetracyclines during the first month of infection was lethal to some *Wolbachia*-harboring filariae, but not to a filariae that did not harbor *Wolbachia*, and treatment of *Wolbachia*-harboring filariae suppressed microfilaremia. Similar prophylaxis studies with *D. immitis* have not been reported, but in one study, tetracycline treatment of heartworm-infected dogs resulted in infertility in the female worms. These bacteria also have been implicated in the pathogenesis of filarial diseases, possibly through their endotoxins. Recent studies have shown that a major surface protein of *Wolbachia* (WSP) induces a specific IgG response in hosts infected by *D. immitis*. It is hypothesized that *Wolbachia* contribute to pulmonary and renal inflammation through its surface protein WSP, independently from its endotoxin component. Studies to determine the effects of suppressing *Wolbachia* populations with doxycyline prior to adulticide therapy will be required to determine the clinical utility of this therapeutic approach.

### CONFIRMATION OF ADULTICIDE EFFICACY

Clinical improvement is possible without completely eliminating the adult heartworms. Worms that do survive adulticide treatment are invariably the antigen-producing females. Previously microfilaremic dogs with post-adulticide, female unisex infections eventually become occult, with or without microfilaricide treatment. Consequently, clinical improvement and successful clearance of microfilariae from the blood do not verify a complete adulticide effect. Recurrence of microfilaremia months later generally is indicative of re-infection.

Heartworm antigen testing is the most reliable method of confirming the efficacy of adulticide therapy. If all of the adult female worms have been destroyed, heartworm antigen should become undetectable by six months post-treatment. The follow-up antigen test can also help differentiate between a persistent infection and re-infection if an antigenemia is detected again at a later date.

Since adult worms may continue to die for more than a month following adulticide administration, dogs that are still antigenemic at five months post-treatment should be allowed more time to clear antigen before retreatment is considered. The health risk of a few residual heartworms should be assessed on an individual case basis, since complete elimination does not assure further clinical improvement. Factors to consider before electing retreatment are the general health of the patient, age in relation to life expectancy, and the performance expectations for the dog. Before committing to retreatment there should be a strong expectation that addition benefit will be achieved.

### ELIMINATION OF MICROFILARIAE

Prior to the introduction of the macrocyclic lactones, elimination of circulating

microfilariae was the second step in the stage-specific sequential treatment (adult, microfilariae, precardiac larvae) of heartworm infection. Today, the broad life-cycle filaricidal activity of the macrocyclic lactones has generally reduced microfilaricide treatment to a by-product of chemoprophylaxis. Controlling the spread of heartworms entails decreasing the reservoirs of infection in the dog population and the benefits of doing so have been cited (see HEARTWORM CHEMOPROPHYLAXIS). However, the rapidity with which this is accomplished is less important than eventually achieving the goal.

Attempts to clear circulating microfilariae prior to completion of adulticide therapy are not usually immediately successful. Microfilariae are eliminated eventually, even from non-adulticide treated dogs, after several months of treatment with prophylactic doses of the macrocyclic lactones (see RETESTING: Monthly Ivermectin, Milbemycin Oxime, Moxidectin and Selamectin). Administration of a macrocyclic lactone should begin as soon as the dog is diagnosed with a heartworm infection.

No drugs are approved currently as microfilaricides by the U.S. Food and Drug Administration. However, under the Animal Medicinal Drug Use Clarification Act of 1994, licensed veterinarians are permitted extra-label use of certain drugs having an established clinical application, if a valid veterinarian-client-patient relationship exists. The dispensing veterinarian is personally responsible for ensuring administration of the proper dose and providing appropriate aftercare when products are used in an extra-label application. The use of monthly administered heartworm chemoprophylactics as microfilaricides is governed by this regulation.

The macrocyclic lactones are the safest and most effective microfilaricidal drugs to become available to date. All are effective at the prescribed prophylactic doses. It is both unnecessary and dangerous to use livestock preparations of these drugs to achieve higher doses for the purpose of achieving more rapid results. Of the products formulated for dogs, milbemycin oxime is the most potent microfilaricide at its label dose and produces the most rapid rate of clearance. If prompt termination of a dog's reservoir potential following adulticide treatment is considered important, this can be achieved most rapidly with milbemycin oxime. Monthly administered macrocyclic lactones allow the flexibility of shortening the customary intervals between treatments (perhaps to two weeks) in order to accelerate removal of microfilariae. The rapid death of large numbers of microfilariae during the early elimination phase, 4-8 hours following the first dose, can cause systemic side effects such as lethargy, inappetence, salivation, retching, defecation, pale mucous membranes and tachycardia. If reactions occur, most are transient and the signs usually are too innocuous to be appreciated. Occasionally, however, a dog with microfilaremia as low as 5000 mf/ml develops acute circulatory collapse.

Prompt treatment with parenteral fluids and one or two shock therapy doses of glucocorticosteroids is an effective antidote. Close observation of higher risk dogs is advised for the first 8-12 hours following administration of microfilaricidal drugs at doses that produce a rapid reduction in circulating microfilariae. This precaution becomes unnecessary for subsequent doses since the pool of microfilariae will have been depleted below the critical level.

When elimination of microfilariae is accomplished in the course of heartworm chemoprophylaxis, a microfilaria test should be performed in adulticide-treated dogs at the time the antigen test is conducted six months post-treatment. If an accelerated rate of clearance is sought, earlier microfilaria testing after two to three macrocyclic lactone doses (repeated as deemed appropriate) is reasonable. For dogs with patent infections administered only chemoprophylaxis, microfilaria testing prior to beginning the next seasonal treatment cycle is recommended.

*These guidelines are based on the latest information on heartworm disease. In keeping with the objective of the Society to encourage adoption of standardized*

*procedures for the diagnosis, treatment and prevention of heartworm disease, they will continue to be updated as new knowledge becomes available.*

*These guidelines have been peer reviewed by independent experts.*