

DIAGNOSIS,
PREVENTION,
and
MANAGEMENT
of

HEARTWORM
(Dirofilaria immitis)
INFECTION
in DOGS



Prepared and approved by the Executive Board of the American Heartworm Society

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Diagnosis, Prevention, and Management of Heartworm (*Dirofilaria immitis*) Infection in Dogs

Preamble

These recommendations are based on the latest information presented at the 2007 Triennial Symposium of the American Heartworm Society (AHS), new research and additional clinical experience. Guidelines for diagnosis, treatment and prevention of heartworm infection in cats are contained in a separate document.

Highlights

Diagnostics: AHS recommends annual testing for canine heartworms.

Chemoprophylaxis: AHS recommends year-round administration of chemoprophylactic drugs to prevent heartworm disease, increase compliance and control pathogenic and/or zoonotic parasites.

Adulticide therapy: AHS recommends use of the “alternate (three-injection) protocol” for treatment of heartworm disease in both symptomatic and asymptomatic dogs.

EPIDEMIOLOGY

Heartworm infection in dogs has been diagnosed around the globe, including all 50 of the United States of America (USA). In the USA, its territories and protectorates, heartworm is 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; however there are regions in central Alaska that have mosquito vectors and climate conditions to support the transmission of heartworms for brief periods. Thus, the introduction of microfilaremic dogs or wild canids could set up a nidus of infection for autochthonous transmission of heartworm in this State. Such re-location of microfilaremic dogs and expansion of the territories of microfilaremic wild canids in other areas of the USA continue to be important factors contributing to further dissemination of the parasite, as 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.

Environmental changes created by humans, changes in natural climatic conditions, and animal movement have increased heartworm infection potential. Commercial and residential real estate development of non-endemic and low incidence areas has led to the spread and increased prevalence of heartworms by altering drainage of undeveloped land and by providing water sources in new urban home sites. In the western USA, irrigation and planting of trees have expanded the habitat for *Aedes sierrensis* (western knot hole mosquito), the primary vector for transmission of heartworms in those states. *Aedes albopictus* (Asian tiger mosquito), which was introduced into the southeastern United States in 1987, has now spread north approaching Canada and has extended past the Rocky Mountains to the west coast. This urban-dwelling mosquito is able to reproduce in small containers such as flower pots. In the northern half of the United States, urban sprawl has led to the formation

of “heat islands”, as buildings and parking lots retain heat during the day and subsequently radiate it during the night. This can potentially create microenvironments that support development of heartworm larvae in mosquito vectors during colder months, thus lengthening the transmission season.

As these vectors expand their territory the number of unprotected animals infected will continue to increase. A pivotal prerequisite for heartworm transmission is a climate that provides adequate temperature and humidity to support a viable mosquito population, and sustains sufficient heat to allow maturation of ingested microfilariae to infective, third-stage larvae (L₃) within this intermediate host. It has been shown under laboratory conditions in three mosquito species that maturation of larvae within mosquitoes ceases at temperatures below 57°F (14°C) and similar activity is expected in other mosquitoes capable of transmitting heartworms. Heartworm transmission does decrease in winter months but micro-environments commonly present in urban areas virtually ensure that the risk of heartworm transmission never reaches zero. Some species of mosquitoes overwinter as adults. While heartworm larval development in mosquitoes may cease in cool temperatures, development quickly resumes with subsequent warming.

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 usually July and August. Models predict that heartworm transmission in the continental USA is limited to six months or less above the 37th parallel, i.e., Virginia-North Carolina State line. Furthermore, predictive risk maps have been produced coupling these basic models with Geographic Information Systems (GIS) based on a thermal regimen and information about mosquito vectors. While these model-based predictions are academically appealing, they do not yet consider several potentially important factors, such as the influence of

microclimate and the unique biological habits and adaptations of the numerous mosquito vectors on larval development.

Once a reservoir of microfilaremic domestic and wild canids is established beyond the reach of veterinary care, the ubiquitous presence of one or more species of vector competent mosquitoes makes transmission possible and eradication becomes improbable.

BIOLOGY AND LIFE CYCLE

The domestic dog and some wild canids are the normal definitive hosts for heartworms and thus serve as the main reservoir of infection. However, even less suitable hosts such as cats and ferrets occasionally have low-level, transient microfilaremias and therefore may serve as a source of infection for mosquitoes during these short periods of microfilaremia.

The life cycle of *D. immitis* is relatively long (usually 7-9 months) compared with most parasitic nematodes. The susceptible mosquito becomes infected when taking a blood meal needed for egg development from a microfilaremic host. The microfilariae develop to the third stage in the mosquito's malpighian tubules and then migrate via the body cavity to the head and mouthparts of the mosquito where they become infective. The time required for the development of microfilariae to the infective stage in the mosquito is temperature-dependent. At 27° C and 80% relative humidity, development takes about 10-14 days.

Infective, third-stage larvae (L₃) are deposited in a droplet of hemolymph (mosquito blood) on the host while the mosquito is taking a blood meal. Immediately after the blood meal, these sexually differentiated L₃ enter the animal's body via the puncture wound in the skin made by the mosquito's mouthparts. Three days after experimental subcutaneous injection of the L₃ in the inguinal region of the dog, most of the larvae are found in the subcutaneous tissues near their entry site. By day 21, most of the larvae have migrated to the abdominal tissues of the dog, and by day 41, they may be recovered from either the abdominal or thoracic tissues. Apparently L₃ and L₄ travel between muscle fibers during migration, whereas juveniles (immature adults) penetrate muscle and eventually veins, transporting them toward the heart and lungs. The molt from L₃ to L₄ begins as early as day 3 and ends as late as day 9-12. L₄ molt to the final stage at day 50-70. Worms reach the pulmonary vasculature as early as day 70 and all have arrived by day 90-120. The first worms entering the pulmonary vasculature on day 70-85 are 1-1.5 inches in length. Thereafter the female worms will increase in length by almost tenfold. They become sexually mature about day 120 post infection. Dogs develop patent infections (i.e., have microfilariae

circulating in their blood) as early as 6 months but usually by 7-9 months post-infection.

When juvenile heartworms first reach the lungs, the blood pressure forces them into the small pulmonary arteries. As they grow and increase in size, they progressively occupy larger and larger arteries until they become fully mature. The eventual location of the mature adult worms appears to depend mainly on the size of the dog and the worm burden. A medium-sized dog (e.g., Beagle) with a low worm burden (i.e., 10) usually has worms mainly in the lobar arteries and main pulmonary artery. As the worm burden increases, worms are also located in the right ventricle. Dogs with more than 40 worms are more likely to have caval syndrome, where most of the worms migrate into the right ventricle, right atrium and the caudal vena cava, thus interfering with valvular function and/or blood flow.

A clear understanding of heartworm transmission, development, prepatent period, and the susceptibility of the different life stages to the parasite to available pharmaceutical drugs is critical. This knowledge base is necessary to effectively select the most appropriate adulticide treatment option and treatment time, and to develop realistic expectations for the veterinarian and client for the outcome of therapy.

PRIMARY DIAGNOSTIC SCREENING

Test Timing for Optimal Results

Currently available heartworm antigen tests detect protein secreted mainly by adult female *Dirofilaria immitis* and the most useful microfilaria tests concentrate microfilariae and allow for more accuracy in identifying the filarial species. The earliest that heartworm antigen and microfilariae can be detected is about five and six months post-infection, respectively. Antigenemia may precede, but sometimes lags the appearance of microfilariae by a few weeks. Antigen may never be detected or only sporadically detected in dogs with very low worm burdens. Also antigenemia may be suppressed until about nine months post infection in heartworm positive dogs placed on macrocyclic lactone chemoprophylaxis. 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 no need or justification for testing a dog for antigen or microfilariae prior to about seven months of age.

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, and this figure is even higher for dogs on a macrocyclic lactone prevention program. The current generation of heartworm antigen tests identify most “occult” (adult worms present but no circulating microfilariae) infections consisting of at least one mature female worm and are nearly 100% specific. Because less than 1% of infections are patent but not antigenemic, testing only for microfilariae is not recommended.

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 are minor. False negative results also can occur rarely with any one test, so unexpected negative results should be followed by retesting with a different test. Specificity is consistently very high with all the antigen tests, and this is an 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 confounding complications such as the transient increase in antigenemia associated with recent worm death or low antigen levels from infections with young adult female worms and/or only a few adult females. 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 coupled with 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 different antigen test format. Concentration tests for microfilariae, thoracic radiography to detect signs of heartworm disease or ultrasonographic visualization of worms may also validate weakly positive antigen test results. In addition, upon request, most test manufacturers will analyze ambiguous samples in their own laboratories. In cases of minimal 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 instructions have not been followed. 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 positive antigen test results.

Microfilaria Tests

Most microfilaremic dogs can be detected by microscopically examining fresh blood for microfilariae or 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 USA.

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, at least 1.0 ml of blood should be examined using a concentration technique (modified Knott test or filtration test) to determine the absence or presence of microfilariae. 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, identifies the patient as a reservoir of infection and alerts the veterinarian to potential severe reaction if administering a microfilaricide to a dog with a high microfilarial count.

HEARTWORM CHEMOPROPHYLAXIS

Canine heartworm infection is preventable, despite the inherently high susceptibility of dogs. Since dogs living in heartworm endemic areas are at risk, chemoprophylaxis is a high priority. Puppies should be started on chemoprophylaxis

as early as possible, preferably no later than eight 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.

Even though continuous, year-round, transmission may not occur throughout the country, year-round use of broad-spectrum chemoprophylaxis products with endoparasitic and/or ectoparasitic activity during this extended period should enhance compliance and assists in preventing pathogenic and/or zoonotic parasitic infections.

Options for effective chemoprophylaxis include several drugs administered either in oral, topical or parenteral formulations at a monthly or six-month interval. Before starting a prophylactic regime, all mature dogs that may have been infected for seven months or longer 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 in a dog seven months of age or older. This will avoid unnecessary delay in detecting sub-clinical infections and potential confusion concerning effectiveness of the prevention program should a pre-existing infection become 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 records of past treatment and testing do not exist, it is advisable to test the patient before dispensing or prescribing chemoprophylaxis.

Macrocytic lactones

The most commonly used heartworm chemoprophylactics are the macrocyclic lactones (ivermectin, milbemycin oxime, moxidectin and selamectin). These drugs have excellent therapeutic/toxic ratios and possess anthelmintic activity against microfilariae, third- and fourth- stage larvae, and in some instances of continuous use, young adult heartworms. The filaricidal effect of oral and topical formulations on precardiac larvae can be achieved by brief pulsing at low doses, which makes these drugs virtually 100% effective when given following label instructions and among the safest used in veterinary medicine.

All oral and topically administered macrocyclic lactone chemoprophylactic products are labeled for a monthly dosing interval. Thereafter, efficacy against late fourth-stage larvae declines and is unpredictable. Juvenile worms, which can be found as early as 52 days post infection, are even less susceptible to chemoprophylaxis. As worms age, they require progressively longer-term administration to achieve a high level of protection. The extended post-infection efficacy of the macrocyclic lactones is a partial safeguard in the event of inadvertent delay or omission of regularly scheduled doses but does not justify lengthening the recommended one month interval of administration for the oral and topical formulations.

The extent of efficacy against late fourth-stage larvae and juvenile worms has important implications for chemoprophylaxis in dogs that have either missed doses during the transmission season, or are already into the transmission season before chemoprophylaxis is started and may already be infected. Short lapses in administration may not result in mature infection, particularly in areas where challenges are low and seasons when transmission potential is lowest. However, lapses in medication during the transmission period that exceed 4 weeks will increase a dog's risk of infection; therefore, continued monthly prophylaxis throughout the year even in cooler climates has merit and may provide substantial protection. In fact, dogs of some compliant owners still become infected.

Some Collies and other p-glycoprotein deficient dogs are unusually sensitive to a variety of commonly used veterinary drugs. The macrocyclic lactones, the only chemical class of drugs currently used for heartworm prevention, are included in this list. This sensitivity was first seen with high doses of ivermectin (in excess of 16 times the minimum effective prophylactic dose) but toxicosis has been reported with overdosing 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. The standard chemoprophylactic doses of medications specifically approved for dogs have been shown to be safe in all breeds.

Oral administration: 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, heartworm prophylaxis should be given year-round, but if seasonal treatment is chosen, administration should begin within one month of the anticipated start of transmission and the last dose should be given until one month after transmission ceases.

Topical administration: Moxidectin and selamectin are available as a topically applied liquid. The parameters for treatment with topical products are the same as for monthly oral chemoprophylaxis.

Parenteral administration: A single dose of the slow-release (SR) formulation of subcutaneously injected moxidectin-impregnated, lipid microspheres provides continuous protection in excess of six months. Moxidectin SR should be administered within one month of exposure to infective mosquitoes. Treatment every six months is recommended for maximal protection, but in areas where the risk of infection is limited to five to six months, a properly timed injection of moxidectin SR should provide a comfortable margin of protection. This injectable formulation is not approved in the USA for use in dogs younger than six months of age.

Moxidectin SR was voluntarily removed from the U.S. market in September 2004 for issues related to safety; however, the product was not withdrawn from the market in other countries. With the return of this product to the U.S. market in June of 2008, the U.S. Food and Drug Administration put certain restrictions in place. These restrictions are described in a Risk Minimization Plan (RiskMAP) based on programs used for human drugs. The RiskMAP is an educational program for veterinarians that covers the risks and benefits of the drug and provides information about the product to pet owners. The effort includes comprehensive veterinarian training, pet owner education and consent forms, and specific requirements for the purchase and administration of the product.

Reports of Lack of Efficacy

Lack of efficacy (LOE) of a heartworm preventive product is defined by the Center for Veterinary Medicine of the Food and Drug Administration (FDA) in the USA as a dog testing heartworm positive while consistently receiving heartworm prevention. There are many possible reasons for reports of LOE, including failure to administer sufficient preventive, failure to administer the preventive at the appropriate time interval, failure of a dog to retain a dose and failure of absorption of active ingredient. There is also biological variation in how hosts within the same species metabolize a drug as well as how parasites respond to a drug. Thus, the exact cause of a reported LOE of a product is extremely difficult to determine.

Most LOE claims can be explained by compliance issues, either between the clinic and the client or the client and the pet. It is possible for an animal to become infected by missing or receiving a delayed administration of just one dose of a heartworm preventive product. The likelihood of this occurring

is increased in endemic areas where infection challenges are exceptionally high when compared with other sections of the USA. Highly endemic areas typically have warm temperatures most of the year, an abundance of standing water and substantial mosquito populations. Many of these areas also have large populations of wild canids, with most of the animals infected with heartworms providing a large reservoir of infection. In addition, manufacturers have improved the sensitivity of heartworm antigen tests during the past decade and more animals with low female worm burdens are now being detected.

The increase in the number of LOE reports to the FDA during the past several years has led to concerns of possible heartworm resistance to the current heartworm preventives. First, it is important to understand that parasites do not become resistant to drugs, but rather, product use under specific conditions inadvertently selects worms with resistance genes. These populations of surviving worms are called resistant strains. Some conditions are known to favor the selection of resistant strains, as occurs with trichostrongylid nematodes of small ruminants and with horn flies. Limited refugia (i.e., worms with wild-type genes), a direct life cycle, treatment of entire groups of confined individuals, and the presence of heavy parasite burdens reduce the refugia and support the concentration of selected, resistant genes. Thus, the shorter the life cycle of the parasite, the more rapidly the resistant-gene-selection process proceeds.

If we examine heartworm infection using the same selection factors, we see a converse scenario. Factors such as a long life cycle, relatively light worm burden, an indirect life cycle with mosquitoes as vectors, a large refugia of infected but untreated pets and wild canids that roam freely throughout their territories, treatment of dogs singly rather than in large groups, and pets that travel widely with their owners do not favor the selection of resistant strains. The epidemiology, treatment patterns and abundance of refugia of parasites such as heartworms ensures the wide distribution of large populations of heartworms that are not under strong selection pressure, and their wild-type genes serve to dilute any resistance genes that exist in geographically different worm populations. These conditions greatly decrease the likelihood of widespread emergence of resistant heartworm strains and any resistant strain would likely remain localized.

Professional and client education are perhaps the most important factors to consider in addressing the reports of apparent lack of efficacy of preventive products. The complex biology of the parasite, the effect of changing environmental conditions that affect vector populations, the dynamics of host (wild and domestic) populations, and even the dynamics of human interactions with their pets are also relevant. In the face of the many variable factors, it is critical that veterinary

practices ensure that clients understand the risk of heartworm infection in their area and provide their pets with appropriate heartworm prevention, i.e., consistent year-round administration of preventives.

TESTING CONSIDERATIONS: ANNUAL TESTING AND RETESTING

Annual testing is an integral part of ensuring that prophylaxis is achieved and that more timely treatment can be provided to dogs that test positive in order to minimize pathology.

Testing Considerations Following Noncompliance and When Changing Products

In instances of noncompliance or changing the brand or type of heartworm preventive, it is important to first ensure that the dog is free of heartworm infection. The dog should be tested prior to starting or changing products. A positive test at this time indicates earlier infection. Typically, most practitioners retest at six months to coincide with refilling prescriptions and performing semiannual exams. A positive antigen test at this time is most likely due to an infection acquired before starting or resuming preventive therapy; however, in rare instances, existing infection may be missed (i.e., false negative test due mainly to young- or low-worm-burden infection). Therefore, subsequent antigen testing should be performed on the one-year anniversary date of the initial test and annually thereafter.

If a practitioner wants to more precisely determine if a dog is infected when starting, resuming, or changing any preventive therapy, testing can be performed at this time and again four months later. When one considers that an antigen test may be positive as early as five months after infection and most dogs are positive by nine months after infection, a positive antigen test before dosing is started (or resumed) and/or four months later clearly indicates that the dog was infected prior to initiating (or resuming) dosing or changing products. However, it is important to note that a negative antigen test at four months is highly supportive but does not ensure that a dog was negative for heartworms at the time of starting, resuming or changing any preventive therapy. To minimize the potential for a false-negative test at four months, a second antigen test can be performed one to five months later. A positive antigen test at this later time cannot be unequivocally attributed to earlier or later infection; however, the earlier in this five-month period the test is positive, the more likely infection was acquired prior to initiating (or resuming) dosing or changing products.

Testing of Dogs on Macrocyclic Lactone Preventives

Consistent macrocyclic lactone (ivermectin, milbemycin oxime, moxidectin or selamectin) chemoprophylaxis will eventually clear microfilariae from the blood of most dogs with patent infections. This is achieved by the drugs' ability to exert a direct or indirect microfilaricidal effect, depending on the specific product used, and retard repopulation by gradually suppressing embryogenesis. Consistent dosing will usually eliminate microfilariae within six to 12 months of oral dosing with monthly macrocyclic lactones or one month following moxidectin SR injection. 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.

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 cardiopulmonary disease secondary to heartworm infection. 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 (caudal) lobes. These findings are accompanied by variable degrees of pulmonary parenchymal disease. The earliest and most subtle pulmonary arterial changes are most commonly 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. In the worst cases, eventually the right heart 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 caval syndrome.

PREADULTICIDE EVALUATION

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

The most important variables influencing the probability of post-adulthood thromboembolic complications and the outcome of treatment are the extent of concurrent pulmonary vascular disease, the severity of infection and the activity level of the dog. Assessment of cardiopulmonary status is indispensable for evaluating a patient's prognosis. Post-adulthood 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.

PRINCIPLES OF TREATMENT

Successfully treating heartworm disease in asymptomatic patients or those exhibiting signs of mild disease usually is straightforward, but occasionally can be demanding. Those with moderate or severe heartworm disease or patients with concurrent disease are especially challenging (See SUMMARY OF CLINICAL SIGNS OF CANINE HEARTWORM DISEASE).

The goals of any heartworm treatment are to improve the clinical condition of the animal and to eliminate all life stages of the heartworms (microfilariae, larval stages, juveniles and adults) with minimal post-treatment complications. Dogs exhibiting significant clinical signs of heartworm disease should

Summary of Clinical Signs of Canine Heartworm Disease

Early infection	Class 1	No signs
Mild disease	Class 1	Cough
Moderate disease	Class 2	Cough, exercise intolerance, abnormal lung sounds
Severe disease	Class 3	Cough, exercise intolerance, dyspnea, abnormal heart and lung sounds, enlarged liver (hepatomegaly), syncope (temporary loss of consciousness from reduced blood flow to the brain, ascites (fluid accumulation in the abdominal cavity), death
Caval Syndrome	Class 4	Sudden onset of severe lethargy and weakness accompanied by hemoglobinemia and hemoglobinuria

be stabilized before administering an adulticide. This may require administration of glucocorticosteroids, diuretics, vasodilators, positive inotropic agents and fluid therapy.

A thorough understanding of the host–parasite relationship is necessary to effectively manage heartworm cases. As expected, the number of worms has an effect on the severity of disease, but of equal, if not greater, importance is the activity level of the dog. Controlled studies have shown that dogs infected by surgical transplantation with 50 heartworms and exercise-restricted took longer to develop clinical disease and developed less pulmonary vascular resistance than dogs with 14 heartworms that were allowed moderate activity. This was also evident in naturally infected dogs where there was no correlation between the number of heartworms and pulmonary vascular resistance and is an indication that the host–parasite interaction plays a significant role in the severity of disease. A subsequent study reported similar findings in dogs being treated with melarsomine.

Whereas live heartworms can cause endarteritis and muscular hypertrophy of arteriole walls especially in the caudal pulmonary arteries, dying and dead heartworms cause a significant portion of pathology seen in clinical disease. As worms die from either natural causes or as a result of administration of adulticidal drugs, they decompose and small worm fragments lodge in the distal pulmonary arteriole and capillary beds in the caudal lung lobes blocking blood flow. These worm fragments along with the elicited inflammation and platelet aggregation result in thromboembolisms. During periods of increased activity or exercise, the increased blood flow to these blocked vessels

can cause capillary delamination, rupture and subsequent fibrosis. This leads to increased pulmonary vascular resistance and potential right-sided heart failure. This illustrates a direct correlation between the activity level of the dog and the severity of disease.

ADULTICIDE THERAPY

Melarsomine Dihydrochloride

Melarsomine, administered via deep intramuscular injection into the belly of the epaxial lumbar muscles, is the only adulticidal drug approved by the FDA for heartworm treatment. 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 for administration is imperative. Exercise restriction during the recovery period is essential for minimizing cardiopulmonary complications (see Pulmonary Thromboembolism).

Melarsomine has not been shown to have any activity against worms less than 4 months old. The two-injection protocol (i.e., two injections of 2.5 mg/kg body weight 24 hours apart) listed on the product insert for treating class 1 & 2 heartworm disease kills only about 90% of the adult worms. The three-dose alternate protocol (one injection of 2.5 mg/kg b. wt. followed at least one month later by two injections of the same dose 24 hours apart) listed for treating class 3 heartworm disease kills 98% of the worms. **These overall efficacy values reflect the percentage of**

worms killed in groups of dogs and not the percentage of dogs cleared of worms, which are considerably lower than these overall efficacy values.

Staging of the disease and use of the two-injection protocol has failed to adequately ensure treatment success. Therefore, regardless of the stage of the disease, the three-injection alternative protocol is the treatment of choice of the American Heartworm Society and several university teaching hospitals, due to the increased safety and efficacy benefits and decreased possibility that further treatment with melarsomine would be necessary. Furthermore, 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 is reduced.

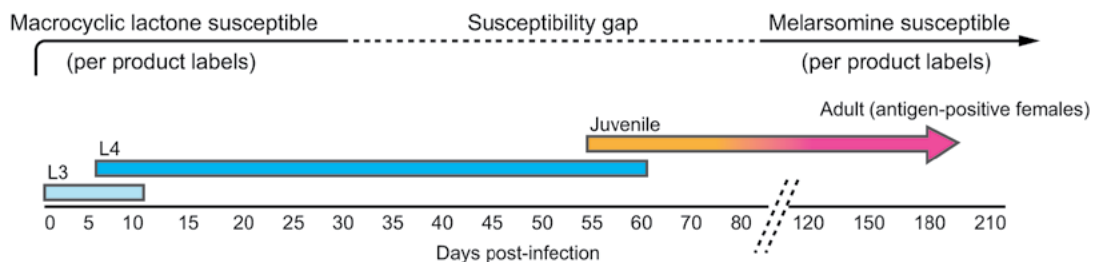
ADJUNCT THERAPY

Macrocytic Lactones

It is highly probable that a heartworm-positive dog has heartworms ranging in age from less than one month to as much as seven years old. Melarsomine’s lack of efficacy against stages less than four months old presents a problem in achieving the goal of eliminating all of the worms. The figure below illustrates the susceptible and non-susceptible ages of heartworms to macrocytic lactones and melarsomine based upon the age of the worm in days (See figure TIMELINE).

This gap can be eliminated by administering a macrocytic lactone preventive for two to three months prior to administering melarsomine. This will eliminate the migrating larvae less than

Timeline of *D. immitis* development, showing periods of susceptibility to macrocytic lactones and melarsomine



The dotted line represents the “treatment gap”, when *D. immitis* are not considered to be susceptible to either treatment.

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two months old and allow those worms between two and four months of age to reach an age at which they are susceptible to melarsomine.

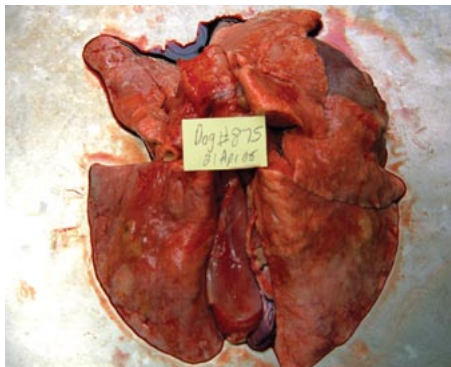
While controversial due to the theoretical risk of selecting heartworm populations that are resistant to macrocyclic lactones, it is beneficial to administer a macrocyclic lactone for up to three months prior to administration of melarsomine, when the clinical presentation does not demand immediate intervention. The logic for this approach is to kill susceptible heartworm larvae and thus prevent re-infection of the dog, while allowing less susceptible juvenile worms, the opportunity to develop into more susceptible adult worms. This tactic increases the chance for removal of the existing heartworm infection when the adulticide injections are given later. Additional benefits of this protocol are the effects of macrocyclic lactones in greatly reducing, if not eliminating circulating microfilariae, stunting immature *D. immitis* and reducing female worm mass by compromising the reproductive system. Administration for two to three months should result in reduced antigenic mass, which in turn may reduce the severity of pulmonary thromboembolism.

Exercise restriction should be enforced from the time of heartworm diagnosis through the period of treatment and recovery, with the most extreme degree of exercise restriction recommended for the first four weeks following melarsomine administration. Macrocyclic lactones administered as

microfilaricides may cause a rapid decrease in the numbers of microfilariae and should be used with caution in dogs with high microfilarial counts. Pretreatment with antihistamines and glucocorticosteroids will minimize potential reactions.

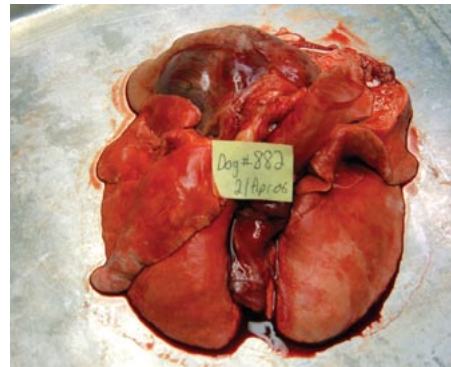
Doxycycline

Many 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-positive 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 also hypothesized that *Wolbachia* contribute to pulmonary and renal inflammation through its surface protein WSP independently from its endotoxin component. Doxycycline is now being evaluated in humans for possible use in the treatment of several filarial diseases and has been the subject of several studies in



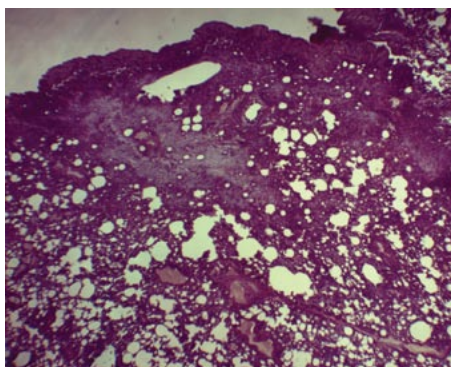
Melarsomine only

Photo courtesy of John McCall, PhD



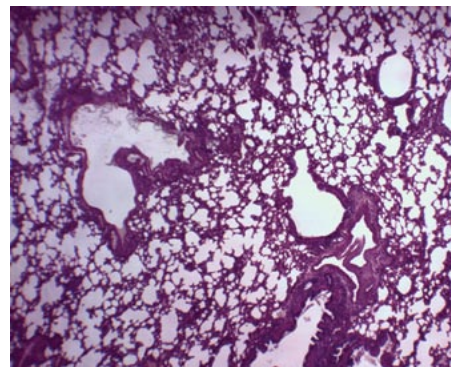
Ivermectin/
Doxycycline/
Melarsomine

Photo courtesy of John McCall, PhD



Melarsomine only

Photo courtesy of Laura Kramer, DVM, PhD



Ivermectin/
Doxycycline/
Melarsomine

Photo courtesy of Laura Kramer, DVM, PhD

heartworm treatment. Studies have shown that heartworm positive dogs pretreated with ivermectin and doxycycline prior to receiving melarsomine injections had less pulmonary pathology associated with the death of the heartworms.

If doxycycline is incorporated into a heartworm treatment protocol it should be given before administration of melarsomine so the *Wolbachia* organisms and their metabolites are reduced or absent when the worms die and fragment. Doxycycline administered at 10mg/kg BID for four weeks has been shown to eliminate over 90% of the *Wolbachia* organisms and the levels remain low for three to four months.

ALTERNATIVE THERAPIES

Long-term Macrocyclic Lactone Administration

Continuous monthly administration of prophylactic doses of ivermectin, moxidectin and selamectin is effective in reducing the life span of juvenile and adult heartworms. The older the worms when first exposed to macrocyclic lactones, the slower they are to die. So, the adulticidal effect of macrocyclic lactones generally requires more than a year of continuous monthly administrations and may take more than two years before adult heartworms are eliminated completely. In the meantime, the infection persists and continues to cause disease. Therefore, long-term continuous administration of macrocyclic lactones generally is not a substitute for conventional arsenical adulticide treatment.

If arsenical therapy is declined, a lengthy course of prophylactic doses of aforementioned macrocyclic lactones will gradually reduce the number of adult heartworms. Should long-term macrocyclic lactone administration be considered for heartworm-positive dogs, exercise should be greatly restricted and the dog should be examined by a veterinarian at least once every four to six months until confirmed to be free of heartworms.

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. As worsening of radiographic signs may be observed, periodic radiographic evaluations may be useful in monitoring the treatment. Another concern in using macrocyclic lactones long-term in heartworm positive dogs as standalone therapy is selection of resistant strains of heartworms.

Ivermectin/Doxycycline

In cases where arsenicals are contraindicated and the animal's overall condition makes standard adulticidal therapy impractical, the use of a monthly ivermectin-based heartworm preventive along with doxycycline could be considered. It has been reported

that ivermectin and doxycycline administered periodically over 36 weeks resulted in a 78% reduction in adult worm numbers. Moreover, microfilariae from dogs treated with doxycycline that were ingested by mosquitoes developed into third-stage larvae that appeared to be normal in appearance and motility, but these larvae were not able to develop into adult worms, thus negating the risk of selecting for resistant strains. The administration of doxycycline at 10 mg/kg BID for a 4 week period every three to four months should eliminate most *Wolbachia* organisms and not allow them to repopulate.

Herbal Therapies

No "natural" or herbal therapies that have been shown to be safe and effective treatment for heartworm disease.

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 clinically inapparent. A pivotal factor in reducing the risk of thromboembolic complications is exercise restriction during the critical month following the first injection and then again after the second/third injections.

Steroids

Administration of diminishing anti-inflammatory doses of glucocorticosteroids helps control clinical signs of pulmonary thromboembolism. Whereas studies showed a decrease in efficacy of the arsenical thiacetarsamide when glucocorticosteroids were administered, no such problem has been reported with melarsomine. In highly endemic areas where animals are likely to have significant worm burdens, the use of prednisone is advocated by many clinicians. It is routinely dosed at 0.5mg/kg BID for the first week and 0.5mg/kg SID for the second week, followed by 0.5mg/kg every other day for 1 to 2 weeks.

NSAIDs/Aspirin

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.

SURGICAL EXTRACTION OF ADULT HEARTWORMS

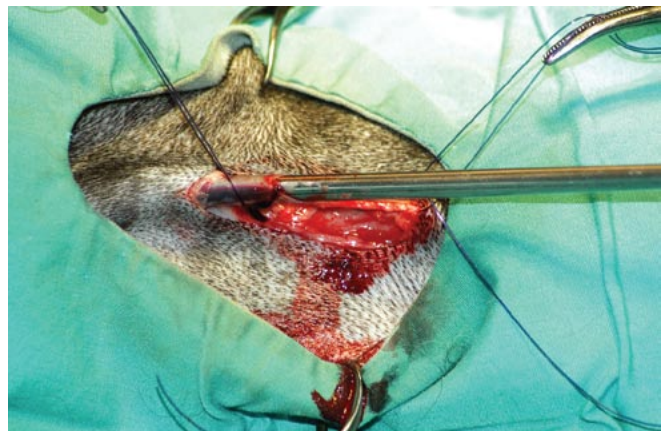
Caval Syndrome (Dirofilarial Hemoglobinuria)

Caval syndrome develops acutely in some heavily infected dogs when 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 and posterior vena cava. The clinical course usually ends fatally within two days, if surgical extraction of the worms is not pursued promptly.

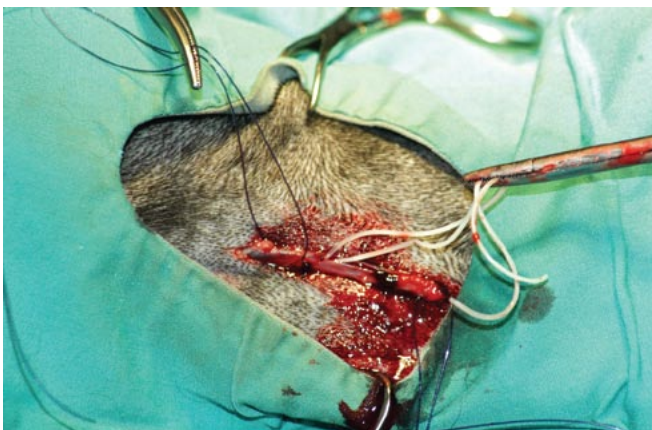
Surgical removal of worms from the right atrium and orifice of the tricuspid valve can be accomplished using light sedation (may not be necessary), local anesthesia and either a rigid or flexible alligator forceps or an intravascular retrieval snare introduced preferentially via the right external jugular vein. With fluoroscopic guidance, if available, the instrument should 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.



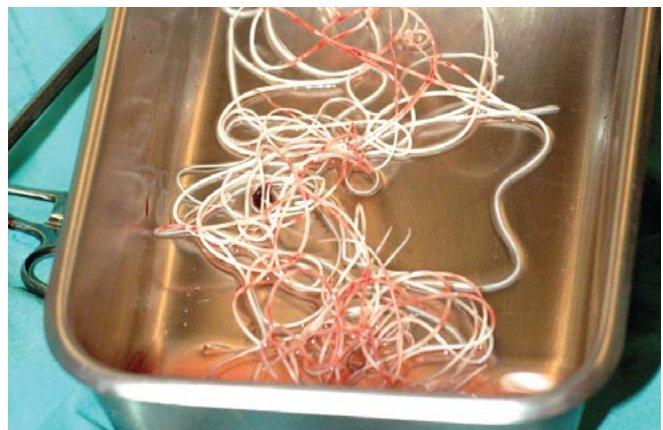
Right external jugular with 1 cm incision, hemorrhage controlled by lifting vein with two loops of #1 nylon suture.



Insertion of 30 cm rigid alligator forcep.



Retrieval of heartworms with multiple passes.



Twenty-four heartworms retrieved from 10 kg JRT.

Photos courtesy of Tom Nelson, DVM

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 of 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.

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. Most microfilaremic dogs with post-adulticide, female unisexual infections become occult within six to nine months, with or without microfilaricide treatment, and particularly if they are on a macrocyclic lactone preventative during and after adulticidal therapy. Consequently, clinical improvement and successful clearance of microfilariae from the blood do not verify a complete adulticide effect. Recurrence of microfilaremia six months later may be due to incomplete clearance of adult worms, maturation of immature worms if a preventive was not given during adulticide therapy or a new infection due to a lapse in chemoprophylaxis.

Heartworm antigen testing is the most reliable method of confirming the efficacy of adulticidal therapy. If all of the adult female worms have been killed, heartworm antigen should become undetectable by six months post-treatment. However, this single test result does not verify that the dog is negative for heartworms, as larval and/or juvenile heartworms may be present in the dog and an insufficient amount of antigen is being produced by these young worms to elicit a positive test result. This is especially critical if a macrocyclic lactone was not administered prior to or initiated concurrently with adulticidal therapy. If a heartworm-positive dog is immediately treated with adulticide and a macrocyclic lactone is not given until three to four weeks after the last dose of adulticide, the dog should have a negative antigen test seven months after the initial dose of macrocyclic lactone before being considered cleared of adult worms.

Since adult worms may continue to die for more than a month following adulticide administration, dogs that are still

antigenemic at any time less than six 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 additional benefit will be achieved.

ELIMINATION OF MICROFILARIAE

No drugs are approved currently as microfilaricides by the U.S. FDA. 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.

Prior to the introduction of the macrocyclic lactones, elimination of circulating microfilariae was the second step in the stage-specific sequential treatment (adult, microfilariae, and precardiac larvae) of heartworm infection. Microfilaricidal treatment was usually done about three weeks after adulticidal therapy, with the understanding that several weekly treatments were often required to completely eliminate circulating microfilariae. The macrocyclic lactones are the safest and most effective drugs for eliminating microfilariae 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. Today, the broad life-cycle filaricidal activity of the macrocyclic lactones has generally reduced microfilaricide treatment to a by-product of chemoprophylaxis. Administration of a macrocyclic lactone should begin as soon as the dog is diagnosed with a heartworm infection.

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. Regardless of the method used for clearing 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 usually 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. Controlling the spread of heartworms entails decreasing the microfilaremic reservoirs of infection in the dog population and the benefits of doing so have been cited (see HEARTWORM CHEMOPROPHYLAXIS).



These guidelines are based on the latest information on heartworm disease and the available treatments. 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.