

Summary of the Current Canine Guidelines for the

Prevention, Diagnosis, and Management of Heartworm (*Dirofilaria immitis*) Infection in Dogs¹

Prepared for and approved by the Executive Board
of the American Heartworm Society²



AMERICAN
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HIGHLIGHTS

- **Diagnostics:** AHS recommends annual antigen and microfilaria testing. (Because the interpretation of diagnostics has become more complex please see the “Microfilaria and Antigen Testing” section for more complete information.)
- **Prevention:** AHS recommends year-round administration of chemoprophylactic drugs to prevent heartworm disease, control pathogenic and/or zoonotic parasites, and enhance compliance, the latter being particularly important in light of the documented presence of resistant subpopulations.
- **Adulticide therapy:** AHS recommends use of doxycycline and a macrocyclic lactone prior to the three-dose regimen of melarsomine (one injection of 2.5 mg/kg body weight followed at least one month later by two injections of the same dose 24 hours apart) for treatment of heartworm disease in both symptomatic and asymptomatic dogs. Any

method utilizing only macrocyclic lactones as a slow-kill adulticide is not recommended.

EPIDEMIOLOGY

Heartworm infection in dogs has been diagnosed around the globe, including all 50 of the United States, and is considered at least regionally endemic in each of the contiguous 48 states and Hawaii. The relocation of microfilaremic dogs and expansion of the territories of microfilaremic wild canids in other areas of the US continue to be important factors contributing to further dissemination of the parasite. Environmental changes created by humans, such as the formation of “heat islands” in the northern US due to urban sprawl, and changes in natural climatic conditions also have increased heartworm infection potential by creating microenvironments that support development of heartworm larvae in mosquito vectors during colder months, thus lengthening the transmission season and virtually ensuring that the risk never reaches zero.

¹These recommendations, revised in July 2014, supersede previous editions and are based on the latest information presented at the 2013 Triennial Symposium of the American Heartworm Society (AHS), new research, and additional clinical experience, and have been peer reviewed by independent experts. The complete version of the 2014 Canine Guidelines can be found at the American Heartworm Society’s website, www.heartwormsociety.org.

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BIOLOGY AND LIFE CYCLE

The domestic dog and some wild canids are the normal definitive hosts for the heartworm, *Dirofilaria immitis*, and thus serve as the main reservoir of infection. Cats and ferrets occasionally have low-level, transient microfilaremia and therefore may serve as a limited source of infection for mosquitoes. A clear understanding of heartworm transmission, development, prepatent period, and the susceptibility of the different life stages of the parasite to available pharmaceutical drugs is critical. For a detailed review of the heartworm life cycle and transmission of heartworm infection, please refer to the complete Canine Guidelines.

HEARTWORM PREVENTION

The AHS recommends year-round heartworm prophylaxis for maximal effectiveness. If seasonal treatment is chosen, administration should begin at least one month prior to the anticipated start of heartworm transmission and depending on the product used, may need to be continued for up to 6 months after transmission typically ceases (see section on Lack of Efficacy). The prescription of heartworm chemoprophylactic medication requires authorization by a licensed veterinarian having a valid relationship with the client and patient. If records of past treatment and testing do not exist, it is necessary to test the patient before dispensing or prescribing chemoprophylaxis. Options for effective chemoprophylaxis include several drugs administered monthly either orally or topically, or parenterally at 6-month intervals. Puppies should be started on preventives as early as possible, and no later than 8 weeks of age. Puppies started on a heartworm preventive after 8 weeks of age should be tested 6 months after the initial dose, then annually thereafter. Before initiating a preventive regime on dogs 7 months of age or older, antigen and microfilariae testing should be performed immediately, then 6 months later, then again in 6 months and annually thereafter. This will avoid delays in detecting subclinical infections and the potential confusion concerning effectiveness of the prevention program if a pre-existing infection becomes evident after beginning chemoprophylaxis.

Macrocyclic Lactones. All heartworm preventives currently marketed belong to the macrocyclic lactone (ML) class of drugs: ivermectin and milbemycin oxime for monthly oral administration; moxidectin and selamectin as topically applied liquids to

be applied monthly; and a slow-release (SR) formulation of subcutaneously injected moxidectin-impregnated lipid microspheres that provides continuous protection for 6 months with a single dose. All orally and topically administered MLs are labeled for a 30-day dosing interval. Thereafter, efficacy against late fourth-stage larvae declines. Juvenile worms, which can be found as early as 52 days post infection, are even less susceptible. The standard chemoprophylactic doses of MLs have been shown to be safe in all breeds, but some Collies and other P-glycoprotein deficient dogs may be unusually sensitive to overdosing. Toxicities with MLs have been reported with overdosing, in combination with other P-glycoprotein inhibiting drugs, or with accidental ingestion of concentrated livestock preparations.

Reports of Lack of Efficacy. Lack of efficacy (LOE) of a heartworm preventive product is considered by the Center for Veterinary Medicine of the US Food and Drug Administration (FDA) as a dog testing heartworm positive regardless of appropriateness of dosage or administration consistency. Most LOE claims are explained by compliance issues including failure to administer sufficient preventive or failure to administer the preventive when it should be given. It is possible for an animal to become infected by missing or delayed administration of just one dose of preventive, particularly in highly endemic areas. Other possible reasons include failure of a dog to retain a dose, failure of absorption of active ingredient, and biological variation in host metabolism of the drug and host immune response to parasites, as well as how parasites respond to a drug. Another consideration for LOE reports may include improved sensitivity of heartworm antigen tests over time possibly resulting in detection of more animals with low female worm burdens.

In the face of the many variable factors, it is critical that all members of the veterinary practice ensure clients understand the implications of heartworm infection and the risk of heartworm infection in their area, and that they are providing their pets with appropriate year-round heartworm prevention. While it is now generally accepted that isolated instances of resistant heartworms have been identified, the extent, the degree of spread, and the reasons for resistance are not understood and are controversial. All agree that owner compliance is the biggest factor in the “failure” of preventives and that the products now available are highly effective and should

continue to be used as the manufacturers suggest. For more on current research on the reported LOE of MLs, please refer to the complete Canine Guidelines.

PRIMARY DIAGNOSTIC SCREENING

Annual testing is an integral part of ensuring that prophylaxis is achieved and maintained. Should an infection be diagnosed, more timely treatment can be provided to minimize pathology and the potential selection of resistant sub-populations.

Test Timing for Optimal Results. Currently available heartworm antigen tests detect protein secreted mainly by adult female *Dirofilaria immitis*. The earliest that heartworm antigen and microfilariae can be detected is about 5 and 6 months post infection, respectively. Antigen may never be detected or only sporadically detected in dogs with very low worm burdens. In addition, antigenemia may be suppressed until about 9 months post infection in infected dogs placed on macrocyclic lactone (ML) preventives. A pre-detection period of at least 7 months should be considered on the day of diagnosis in calculating possible date of infection or duration of infection. Thus, there is no need or justification for testing a dog for antigen or microfilariae prior to 7 months of age.

Microfilaria and 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. It is now recommended, however, that microfilaria testing be done in tandem with antigen testing. This is especially important if there is a high degree of suspicion or if the heartworm prevention history is unknown (e.g., dogs adopted from shelters). It has come to light that in some dogs infected with heartworms, antigen-antibody complexes may lead to false-negative antigen test results. These dogs will be antigen negative and microfilariae positive; a study conducted on shelter dogs in the southeastern United States reported this occurred at a rate of 7.1%. It is important that these dogs are identified and treated to decrease the potential for selection of resistant subpopulations of heartworms. There will be instances where an infected dog is both antigen and microfilariae negative.

Antigen Tests. 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. The tests are nearly 100% specific but subtle differences in sensitivity exist especially in cases with low worm burdens and/or low antigenemia. Currently there are no verified tests capable of detecting infections consisting of only adult male worms. False-negative and false-positive results can occur and unexpected test results should be followed by retesting with a different test or confirmation by a reference laboratory. All positive antigen tests in asymptomatic dogs should be confirmed prior to any adulticide therapy; concentration tests for microfilariae, thoracic radiography, or ultrasonographic visualization of worms may also help validate weakly positive antigen test results. False-negative test results can occur when infections are light, female worms are still immature, only male worms are present, if the test kit instructions have not been followed, and/or if antigen-antibody complexes mask an infection. While laboratory studies have shown that heating serum breaks down these complexes, resulting in more accurate antigen test results, routine heating of blood samples is not recommended at this time as it is contrary to the label instructions for these tests. Therefore, heartworm test results are either “positive” or “no antigen detected” and should NEVER be recorded as “negative.”

Microfilaria Tests. Although screening may be based entirely on antigen testing, antigen-positive dogs should also be tested for microfilariae because microfilariaemia 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. The modified Knott test remains 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*.

Testing Considerations Following Noncompliance and When Changing Products. In these instances, the dog should be antigen tested to determine heartworm status prior to starting or changing products. A positive test indicates pre-existing infection. The dog should *always* be retested 6 months later, and if positive, the infection was most likely acquired before starting or resuming preventive therapy. In rare instances, however, existing infections might still be missed. Antigen and



Figure 1. Testing protocol following known noncompliance.

microfilaria testing should be performed on the one-year anniversary date of the initial test and annually thereafter.

Testing of Dogs on Macrocytic Lactone Preventives.

Antigen testing is the most reliable method of retesting because ML prevention may negate microfilaria testing.

OTHER DIAGNOSTIC AIDS

Radiography provides the most objective method of assessing the severity of heartworm-associated 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, accompanied by variable degrees of pulmonary parenchymal disease. In the worst cases, eventually the right heart enlarges.

Echocardiography can provide definitive evidence of heartworm infection, as well as allow for assessment of cardiac anatomic and functional consequences of the disease. It is not an efficient method of making this diagnosis, however, particularly in lightly infected dogs.

PRE-ADULTICIDE EVALUATION

The extent of diagnostic testing necessary at this point will vary depending on the clinical status of each patient and results of a thorough history, physical examination, and antigen and microfilaria tests. Key factors influencing the probability of post-adulticide thromboembolic complications and outcome of treatment include activity level of the dog, including exercise, excitement, and overheating; the extent of concurrent pulmonary disease as seen on thoracic radiographs; and severity of infection (worm burden). There is no test (or combination of tests) to accurately determine the number of heartworms present, thus every infected pet must be managed as though a substantial heartworm mass is present or a potentially violent individual immune reaction to the dead and dying worms could occur. There is no set protocol for pre-

treatment workup. Adulticide treatments have been successfully performed in numerous cases without the benefit of extensive diagnostic testing; it is probable that treating in the absence of diagnostics, while not ideal, is better than refusing to perform a needed treatment.

PRINCIPLES OF TREATMENT

Treating heartworm infections in asymptomatic patients or those exhibiting signs of mild disease usually is not problematic if exercise is curtailed. Infections associated with moderate or severe heartworm disease or in patients with concurrent disease often are challenging. The goals of any heartworm treatment are to improve the dog's clinical condition and to eliminate all life stages of the heartworms with minimal post-treatment complications. Dogs exhibiting significant clinical signs of heartworm disease should be normalized as much as possible 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 all cases.

ADULTICIDE THERAPY

Melarsomine dihydrochloride is the only adulticidal drug approved by the FDA for heartworm treatment. The AHS recommends the three-dose protocol, one deep intramuscular (IM) injection into the belly of the epaxial lumbar muscles (between L3 and L5) of 2.5 mg/kg body weight followed at least 1 month later by two IM injections of the same dose 24 hours apart in all cases (with the exception of caval syndrome) due to the increased safety and efficacy compared with the two-dose regimen.

Exercise restriction during the recovery period is ESSENTIAL for minimizing cardiopulmonary complications. As worms die as a result of adulticidal treatment, they decompose and worm fragments lodge in the distal pulmonary arteries and capillary beds in the caudal lung lobes blocking blood flow and causing thromboembolism. Increased activity or

exercise increases the blood flow to these blocked vessels, causing capillary delamination, rupture, and subsequent fibrosis, leading to increased pulmonary vascular resistance, pulmonary thromboembolism, and potential right-sided heart failure.

ADJUNCT THERAPY

Steroids. Diminishing anti-inflammatory doses of glucocorticosteroids can help to control clinical signs of pulmonary thromboembolism, which can be severe after adulticide therapy if infection is heavy and pulmonary arterial disease is extensive. Prednisone is routinely dosed at 0.5 mg/kg BID for the first week and 0.5 mg/kg once daily for the second week, followed by 0.5 mg/kg every other day (EOD) 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.

Doxycycline. Many filarial nematodes, including *D immitis*, harbor obligate, intracellular, gram-negative, endo-symbiotic bacteria belonging to the genus *Wolbachia* (*Rickettsiales*). *Wolbachia* have also been implicated as a component in the pathogenesis of filarial diseases. Doxycycline reduces *Wolbachia* numbers in all stages of heartworms. The AHS recommends administration of doxycycline at 10 mg/kg twice daily (BID) for 4 weeks before administration of melarsomine (Table 1). Minocycline given at the same dosage regimen may be a viable alternative during periods of doxycycline shortage.

Macrocytic Lactones. In addition to adult heartworms, a heartworm-positive dog likely harbors juvenile stages of heartworms. The efficacy of melarsomine against juvenile stages (less than 4 months old worms) could present a susceptibility gap, where some stages of *D immitis* might not be susceptible to either the MLs or melarsomine. The susceptibility gap can be minimized by administering an ML preventive for 2 months prior to administering melarsomine. This will reduce new infections, eliminate existing susceptible larvae, and allow older worms (between 2 and 4 months of age) to mature to a point where they would be more susceptible to melarsomine. Reduction of the susceptibility gap can also be potentiated with concurrent use of doxycycline for 30 days, as this

will essentially eliminate all developing larvae during first 60 days of infection. Exercise restriction should be rigidly enforced from the time of diagnosis through the period of treatment and recovery, with the most extreme restriction recommended for 4 weeks following each melarsomine administration. Macrocytic lactones administered as a microfilaricide may cause a rapid decrease in the numbers of microfilariae and should be used with caution in dogs with high microfilarial counts. Topical moxidectin is now FDA-approved for use in heartworm-positive dogs to eliminate microfilariae. No adverse reactions due to high microfilarial counts were observed in the laboratory or field studies conducted for approval of this label claim.

Macrocytic Lactone/Doxycycline. In cases where arsenical therapy is not possible or is contraindicated, the use of a monthly heartworm preventive along with doxycycline at 10 mg/kg BID for a 4-week period might be considered. An antigen test should be performed every 6 months and the dog not considered cleared until two consecutive NAD (no antigen detected) heartworm antigen tests, 6 months apart, have been obtained. If the dog is still antigen positive after one year, repeat the doxycycline therapy. Exercise should be rigidly restricted for the duration of the treatment process.

AHS-RECOMMENDED TREATMENT PROTOCOL

The AHS recommends a multi-modal approach to treating heartworms based on the information presented above and depicted in the following example management protocol (Table 1). A retrospective study of clinical cases comparing the protocol listed in Table 1 with a similar protocol without doxycycline showed a decrease in respiratory complications and mortality rates when doxycycline was included.

SURGICAL EXTRACTION OF ADULT HEARTWORMS

Caval syndrome (dirofilarial hemoglobinuria) develops acutely in some heavily infected dogs when adult heartworms partially obstruct blood flow through the tricuspid valve and also interfere with valve closure and usually ends fatally within 2 days if surgical extraction is not pursued promptly. Diagnosis is based on sudden onset of severe lethargy, dyspnea, pale mucous membranes, and weakness frequently accompanied by hemoglobinemia and hemoglobinuria and a loud systolic murmur of tricuspid regurgitation.

Table 1. AHS-Recommended Treatment Protocol for Heartworm Disease

Day	Treatment
Day 0	Dog diagnosed and verified as heartworm positive: <ul style="list-style-type: none"> • Positive antigen (Ag) test verified with microfilaria (MF) test • If no microfilariae are detected, confirm with 2nd Ag test from a different manufacturer Begin exercise restriction. <ul style="list-style-type: none"> • The more pronounced the signs, the stricter the exercise restriction If the dog is symptomatic: <ul style="list-style-type: none"> • Stabilize with appropriate therapy and nursing care • Prednisone prescribed at 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg EOD 3rd and 4th weeks
Day 1	Administer heartworm preventive. <ul style="list-style-type: none"> • If microfilariae are detected, pretreat with antihistamine and glucocorticosteroid, if not already on prednisone, to reduce risk of anaphylaxis • Observe for at least 8 hours for signs of reaction
Days 1–28	Administer doxycycline 10 mg/kg BID for 4 weeks. <ul style="list-style-type: none"> • Reduces pathology associated with dead heartworms • Disrupts heartworm transmission
Day 30	Administer heartworm preventive.
Day 60	Administer heartworm preventive. First melarsomine injection 2.5 mg/kg intramuscularly (IM) Prescribe prednisone 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg EOD 3rd and 4th weeks. Decrease activity level even further. <ul style="list-style-type: none"> • Cage restriction/on leash when using yard
Day 90	Administer heartworm preventive. Second melarsomine injection 2.5 mg/kg IM
Day 91	Third melarsomine injection 2.5 mg/kg IM Prescribe prednisone 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg EOD 3rd and 4th weeks. Continue exercise restriction for 6 to 8 weeks following last melarsomine injections.
Day 120	Test for presence of microfilariae. <ul style="list-style-type: none"> • If positive treat with a microfilaricide and retest in 4 weeks Establish year-round heartworm prevention.
Day 271	Antigen test 6 months after completion; screen for microfilariae.

The diagnosis is confirmed by echocardiographic visualization of heartworms within the tricuspid orifice and/or posterior vena cava. Adulticide therapy is recommended within a few weeks post-surgery to eliminate any remaining worms.

Pulmonary Arterial Infections. 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. Following echocardiographic assessment of location of the worms, the main pulmonary artery and lobar branches can be accessed with flexible alligator forceps aided by fluoroscopic guidance. Although infrequently performed, worm extraction is the procedure of choice for the most heavily infected and high-risk dogs, and intraoperative mortality is low.

ALTERNATIVE THERAPIES

Long-term Macrocyclic Lactone Administration. Slow-kill methods using continuous monthly administration of prophylactic doses of any ML are NOT RECOMMENDED.

Herbal Therapies. No “natural” or herbal therapies have been shown to be safe and effective prevention or treatment for heartworm disease.

CONFIRMATION OF ADULTICIDE EFFICACY

Clinical improvement and successful clearance of microfilariae from the blood do not verify a complete adulticide effect. Recurrence of microfilaremia may be due to incomplete clearance of adult worms, maturation of immature worms if a preventive was not given prior to and during adulticide therapy, or from a new infection due to a lapse in preventive administration. Heartworm antigen testing is the most reliable method of confirming adulticide efficacy. If all adult female worms have been killed, antigen levels typically fall below detectable limits by 6 months post treatment; however, any larval

and/or juvenile heartworms still present would not be detected. 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 6 months post treatment should be allowed more time to clear antigen before retreatment is considered.

ELIMINATION OF MICROFILARIAE

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 is advisable in the face of high microfilariae burdens to minimize potential reactions. Topical moxidectin is approved by the FDA to eliminate microfilariae.

Current protocols utilizing doxycycline in combination with regular preventive doses of MLs have essentially eliminated the need for post-adulticidal elimination of microfilariae. Administration of a macrocyclic lactone with doxycycline should always begin as soon as the dog is diagnosed with a heartworm infection. A microfilaria test should be performed in adulticide-treated dogs at the time the antigen test is conducted (6 months post treatment).

ELECTIVE SURGERIES ON DOGS WITH HEARTWORM

Veterinarians are frequently faced with the decision whether to perform an elective procedure such as a spay or neuter on a heartworm-positive dog. A study has shown no increase in perioperative complications in heartworm-positive dogs with no to mild clinical signs of heartworm disease. Elective surgical procedures should be avoided in dogs exhibiting symptoms of more advanced disease and treatment utilizing the protocol in Table 1 should be initiated. Surgery can then be performed 6 months after adulticidal treatment if the dog has recovered sufficiently.

