

HEARTWORM DISEASE IN DOGS: AN UPDATE - 2011

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Diagnosis

The diagnosis of heartworm infection (HWI) has been changed in two major ways: 1) the development of superior immunodiagnostic tests has lessened reliance on microfilarial concentration tests (modified Knott and filter tests) which are prone to false negative results; and 2) the realization that HW macrolide preventatives reduce microfilarial concentrations to the point that the only reliable way to test dogs receiving macrolides is using immunological methodologies. Microfilarial tests should still be employed to rule in or out microfilaremia in dogs that test positive to the antigen test. Microfilarial tests are receiving renewed interest because of concerns of developing heartworm resistance which could conceivably result from exposure of microfilaremic dogs to macrocyclic lactones.

Antigen Tests. Today's commercial antigen tests (ELISA and immunochromatographic) measure circulating heartworm antigen and have achieved virtually 100% specificity, making them the screening tests of choice.¹ Sensitivity is also excellent, overall greater than 85%.² This compares favorably with the concentration tests which may yield 5-67% (typically 10-25%) false negatives, depending on the geographic area in question.³ Direct smear and capillary tube tests are generally 5-10% less accurate.⁴ While false positive tests are rare when antigen tests are carefully performed, false negatives do occur, especially in the case of low worm burdens or immature infections. In a study comparing 2 commercial ELISA antigen tests, approximately 50% of results were falsely negative when 1-2 worms were present, but $\leq 10\%$ were negative when 3-5 worms were present, and no false negatives resulted when >20 worms were present.² False negative tests also result from all-male infections, because these tests detect antigens produced by gravid females.⁴ A study by the author tested 3 commercial heartworm kits in dogs with natural infections of low worm burdens. The median sensitivity was 79% in these challenging cases.^{2a} On average, the tests detected as positive 64%, 85%, 88%, and 89% of worm burdens of 1, 2, 3, and 4 adult female worms, respectively. All tests were 97% specific.^{2a}

The ELISA antigen technology also allows semi-quantitation of worm burden and efficacy of adulticide therapy⁴ and has successfully been used to predict antigen load, and hence, approximate worm burden. Rawlings has shown this to be useful in predicting thromboembolic complications, with dogs bearing greater worm burdens being more likely to experience such complications after adulticide.⁵ Since the antigen concentration falls to undetectable levels 8-12 weeks (or longer) following successful adulticide therapy, HW antigenemia persisting beyond 12 weeks post-therapy indicates persistent infection.^{4,6}

As suggested above, macrolide preventative therapy typically results in clearance of microfilaria within 6-8 months after initiation.^{4,6,7} In addition, embryostasis may be permanent.¹ Thus, the use of direct smears, the modified Knott test, and filter tests for **screening** dogs receiving monthly HW preventatives is inappropriate. This fact, and the high efficacy of monthly preventatives, has caused some to question the need for yearly testing.¹ Most authors, however, have disagreed with this stance and recently the Companion Animal Parasite Council and American Heartworm Society have made a formal recommendation for yearly testing.^{7,7a,7b} Nevertheless, the only effective testing modality in dogs receiving monthly preventative is the antigen test.

Microfilaria testing. The microfilarial tests should not, however, be abandoned. There is utility in their use in at least two important ways: 1. to identify microfilariae which might result in an adverse reaction to preventives (see details below); 2. To identify microfilariae which, when treated chronically with preventive dosages of macrolides, may contribute to the development of resistance. Therefore, microfilaria testing should be performed in all antigen-positive dogs.

Radiography. Although not an effective screening test for HWI, thoracic radiography offers an excellent method for detecting HWD, for determining its severity, and for evaluating pulmonary parenchymal changes. Radiographic abnormalities, which develop relatively early in the disease course, are present in approximately 85% of cases. According to the study of 200 heartworm-infected dogs by Losonsky, et al., radiographic features

include right ventricular enlargement (60%), increased prominence of the main pulmonary artery segment (70%), increased size and density of the pulmonary arteries (50%), as well as pulmonary artery tortuosity and "pruning" (50%).²⁶ If heart failure is present, enlargement of the caudal vena cava, liver, and spleen, as well as pleural effusion and/or ascites may be evident. Thrall and Calvert suggested that pleural effusion is uncommon in heart failure due to HWD, demonstrating that marked enlargement of the cranial lobar pulmonary artery was a more sensitive indicator of HWD-associated heart failure than is enlargement of the caudal vena cava.²⁷

Thoracic radiographs obtained in the ventrodorsal projection are preferable for cardiac silhouette evaluation, ease, and often minimizing patient stress. However the dorsoventral projection is superior for the evaluation of the caudal lobar pulmonary vessels which are considered abnormal if larger than the diameter of the ninth rib where the rib and artery intersect. The cranial pulmonary artery is best evaluated in the lateral projection and should normally not be larger than its accompanying vein or the proximal one-third of the fourth rib.

The pulmonary parenchyma can best be evaluated radiographically. With pneumonitis, the findings include a mixed interstitial to alveolar density, which is typically most severe in the caudal lung lobes. In eosinophilic nodular pulmonary granulomatosis, the inflammatory process is arranged into the interstitial nodules, associated with bronchial lymphadenopathy and occasionally, pleural effusion. With pulmonary thromboembolism, the radiographic findings of coalescing interstitial and alveolar infiltrates, particularly in the caudal lung lobes, reflect the increased pulmonary vascular permeability and inflammation described above. Consolidation may accompany massive embolization and/or pulmonary infarction.

Other. Echocardiography may be useful in detecting worms when a high index of suspicion for HWI exists in the presence of negative ELISA and Knott tests.⁸ Heartworms can be identified in the right ventricle or pulmonary artery. In the author's experience, HW spend little time in the heart and can be most often seen as "double linear foreign bodies" in the proximal pulmonary artery. Unfortunately, while highly specific, the finding of HW in dogs using this technique is not consistent (low sensitivity). In caval syndrome, however, the appearance is consistent and characteristic.⁹ A mass of HW can be seen dropping into the right ventricle during diastole, moving back to the atrium in systole. In the appropriate clinical setting, this finding is pathognomonic for caval syndrome.¹⁰ Non-selective angiography can be utilized to prove the presence of non-caval syndrome HWI when all else fails.

With the recognition of Wolbachia organisms living within filarid parasites, new diagnostic tests are possible. Though no validated test has yet been marketed, there is hope that either antigen or antibody tests to Wolbachia may add to our diagnostic armamentarium with this organism acting as a surrogate to *Dirofilaria* residing the animals tested.

Prophylaxis

Prevention of HWI is an obvious and attainable goal for the veterinary profession. Prevention failure results from ignorance on the part of owners as to the presence or potential severity of HWI, lack of owner compliance, or from inadequate instruction on preventative measures by the attending veterinarian.^{1,32-34} Studies of owner compliance have revealed that approximately 55% of dog owners that use veterinary care purchase heartworm preventative, and enough medication is dispensed only to meet the needs of approximately 56% of those dogs. Hence the proportion of "cared for" dogs in the population that receive adequate heartworm prophylaxis is less than one third.³³ If one takes into consideration doses purchased but not administered and dogs that are never taken to a veterinarian, the percentage of protected dogs falls drastically. This was emphasized in North Carolina in 1999, when Hurricane Floyd caused extensive flooding and disruption in the poorest part of the state. Of dogs rescued from the floodwaters, 67% were infected with heartworms (personal communication, Dr. Kelli Ferris, North Carolina State University, 2003). In addition, evidence suggests that the veterinary profession is failing in its education of clients. New and colleagues,³⁵ upon questioning veterinary clients purchasing macrolide preventatives, found that 38% did not realize that their prescribed drug's spectrum was broader than solely preventing HWI.

Macrocyclic Lactone (Macrolide) Antibiotics. The introduction of the macrocyclic lactone endectocides (macrolides), ivermectin (Heartgard[®], Iverhart[®], TriHeart[®]), ivermectin with pyrantel pamoate (Heartgard[®] Plus, Iverhart Plus[®], TriHeart[®] Plus), ivermectin with praziquantel (Iverhart Max[®]), milbemycin oxime (Interceptor[®]), milbemycin with lufenuron (Sentinal[®]) and with spinosad (Trifexis[®]), selamectin (Revolution[™]), and moxidectin (ProHeart[®], ProHeart[®] 6), and moxidectin with imidacoprid (Advantage/Multi[™])

has provided the veterinary profession with highly effective, incredibly safe heartworm preventatives in a variety of formulations and with a variety of spectra (see Table 1). These agents, because they interrupt larval development (L3 and L4) during the first 2 months after infection, have a large temporal window of efficacy and are administered monthly. These products have enjoyed great efficacy, virtually 100%, when used as directed. Recently, a single isolate (MP3) from north-eastern Georgia has shown resistance/tolerance to some macrocyclic lactones, when administered once 30 days after heavy experimental challenge.

All are safe in collies when used as directed at preventive dosages. They each have microfilaricidal efficacy and render female heartworms sterile. Hence microfilarial tests for HWI cannot be reliably used in dogs receiving these products. Prophylaxis should be commenced no later than 6 to 8 weeks of age in endemic areas or as soon thereafter as climatic conditions dictate.^{19,49} Macrolides should be administered precisely as indicated by the manufacturer. If accidental lapses of more than 10 weeks occur, the preventative should be reinstated at recommended doses and maintained for at least 12 consecutive months.²⁵ In the event of a lapse in preventative administration during a time of known exposure risk, an antigen heartworm test should be performed 7-8 months after the last possible exposure to determine if infection has occurred. It is recommended by the AHS and by CAPC that these agents be used year-around in all areas of the U.S.

Off-Label Use. The macrolides are effective microfilaricides, with varying microfilarial kill rates, but microfilariae, in reduced numbers, are often found in the circulation for months after treatment has begun. Recently it has been shown that some macrolides have adulticidal activity if used continuously for prolonged periods.³⁹⁻⁴¹

Macrocyclic Lactone “Resistance/Tolerance”. In 2005, the FDA-CVM reported an increase in the reports of LOEs (Lack of Effectiveness) for macrocyclic lactones and required that such agents no longer be labelled as “perfect” in terms of efficacy. This failure of complete rapid microfilarial clearing, coupled with concern in the Mississippi River delta region (areas of LA, AR, MS, TN), has caused concern that resistance to this class of drugs may be developing. The proof of this is small, but taken together, the data argue that a small percentage of microfilariae, isolated from dogs in this region have characteristics suggesting tolerance to the drug group. A joint consensus of the AHS and CAPC stated the following (excerpts). “There is evidence in some HW populations for genetic variations that are associated with decreased in vitro susceptibility to the macrocyclic lactones. Whether the observed genetic variations constitute heritable resistance is being investigated. Most credible reports of LOE that are not attributable to compliance failure are geographically limited at this time. The extent of the problem is obscured by demonstrated lack of owner and DVM compliance, possible changes in environmental/vector factors, and more effective antigen testing. The potential for resistance is *not* a reason to abandon use of approved preventive products.”

The concern relative to the presence of circulating microfilariae in dogs that are started and maintained on monthly preventives is that they could be a source of propagation of microfilariae that are preselected for resistance to macrocyclic lactones. In 2005, Prichard wrote “Consideration of the proportion of the *D. immitis* population in refugia, the life cycle stage targeted, and the anthelmintic dosages used suggest that it is unlikely that significant avermectin/milbemycin [macrolides] resistance will be selected in *D. immitis* with current treatment strategies.”¹¹⁸ However, this belief was based upon the assumption that people were using the preventives as per label instructions, not using them as adulticides and microfilarial suppressants. The prudent approach is simply to administer the products as approved by the FDA: as preventives that should be given to microfilaria-negative dogs. This means that the “soft” or “slow” kill approach to adulticidal therapy should be avoided. Likewise, one could argue against the use of macrocyclic lactones in microfilaria-positive dogs prior to beginning them on adulticidal therapy (ie, a method advocated by this author; see below) as 10% to 20% of these dogs will have circulating microfilariae for months after they start this regimen – microfilariae that have seen a macrocyclic lactone. If this approach is utilized, the clinician must ensure that microfilaria are eradicated in the first months of macrolide therapy. All current heartworm preventives belong to the same class of molecule, the macrocyclic lactones, and thus, we need to be very prudent in our long-term stewardship of these drugs.

Therapy

Adulticidal therapy. An important breakthrough in the management of heartworm infection (HWI) is the adulticide melarsomine, an organoarsenical superior in safety and efficacy to thiacetarsamide.¹⁷ This product, which

is administered twice, at 2.5 mg/kg q24h, has a mean retention time 5 times longer than thiacetarsemide and its metabolites are free in the plasma, on which HW feed.¹⁸ In a study of 382 dogs with HWI receiving melarsomine, none required cessation of therapy due to hepato-renal toxicity, as compared to 15-30% with thiacetarsemide, the agent previously used.¹⁸ With 2 doses, the efficacy is over 90% (FDA pivotal study) with the useful flexibility of a 50% worm kill with 1 dose. This then allows “split-dose” protocol to be utilized in severely afflicted individuals or in those in which pulmonary thromboembolism (PTE) is a concern. This method allows destruction of only one-half the worms initially (1 IM injection of 2.5 mg/kg), thereby lessening the chance for embolic complications. This single dosage is followed by a 2 dose regimen in 1-3 months, if clinical conditions permit. While the manufacturer recommends this protocol (Figure 1) for severely affected dogs, the author employs it in **all cases** unless there is financial constraint or underlying concern for arsenical toxicity (for example, preexistent severe renal or hepatic disease).^{18a} One disadvantage to the “split-dose” method, in addition to the expense, is the need for 2 months’ exercise restriction.

In 55 dogs, with severe heartworm disease (HWD) and treated in this 3-dose manner, 96% had a good or very good outcome with >98% negative for antigenemia 90 days post-therapy.¹⁸ Although symptomatic and even fatal PTE can result from treatment with melarsomine, no case of severe PTE was seen in the 382 dogs of this series.¹⁹ Of the 55 severely affected dogs, 31% had “mild or moderate PTE”; no fatalities resulted. The most common sign was fever, cough, and anorexia 5-7 days post-treatment. This was associated with mild perivascular caudal lobar pulmonary radiographic densities and subsided spontaneously or after corticosteroid therapy.

The most common complication to melarsomine therapy is the local inflammatory reaction at the injection site. This can be minimized by following the manufacturer’s directions explicitly (change needles before injecting, choose deep IM site with care, put pressure on site after injection, and alternate sites). In addition, corticosteroids (e.g. dexamethasone) or NSAIDs can be given at the time melarsomine is administered to lessen the reaction.

“Soft” or “Slow” Kill. It is now known that certain macrolides have adulticidal properties.^{6,16,20} Ivermectin, when administered for 31 months continuously has nearly 100% efficacy in young heartworm infections.²⁰ It has been shown, however, that lung and pulmonary vascular manifestations of HWD still result when ivermectin “prophylaxis” is begun 5.5 and 6.5 months post-infection and continued for 1 year.²¹ Selamectin, when administered continuously for 18 months killed approximately 40% of transplanted worms.¹⁶ Sustained release moxidectin also appears to have some adulticidal efficacy.¹² Recent data suggests that an aggressive macrolide protocol (ivermectin, given at 6 ug/kg weekly instead of monthly), coupled with a complex regimen of doxycycline (10 mg/kg/day) will hasten worm destruction, with worm eradication with approximately 9 months’ therapy.^{21a} Furthermore, microfilariae are eradicated more quickly in this manner. This has caused many to invoke the use of doxycycline routinely in the management of heartworm infection in dogs. While there may be a role for this therapeutic strategy (Slow Kill) in cases in which patient age, financial constraints or concurrent medical problems prohibit melarsomine therapy, the current recommendations are that **macrolides not be adapted as the primary adulticidal approach.**

Surgery. Surgical removal of HW can minimize PTE, as compared to pharmacologic adulticides, such as melarsomine.^{22,23} This procedure, however, requires specialized training and instrumentation, including fluoroscopic imaging capabilities. Nevertheless, it remains an alternative for the management of high risk patients.

Ancillary therapy. Corticosteroids are indicated in HWD **only** in the face of pulmonary parenchymal complications (including PTE), to treat or prevent adverse reactions to microfilaricides, and to minimize tissue reaction to melarsomine. Early studies demonstrated that corticosteroid therapy reduced pulmonary blood flow and worsened intimal disease in a model of HWI after adulticide.²⁴ For allergic pneumonitis, prednisolone (1 mg/kg/day) is administered for 3-5 days and discontinued or tapered, as indicated.²⁵ The response is generally favorable. Prednisolone has also been advocated for the management of PTE. Because of the potential for fluid retention, steroids should be used cautiously in the face of heart failure.

Antithrombotic agents have received a good deal of attention in the management of HWD.^{24,26-29} Potential benefits include reduction in severity of vascular lesions of HWD, reduction in pulmonary arterial vasoconstriction and pulmonary hypertension, as well as minimization of post-adulticidal PTE. Aspirin has shown success in diminishing the vascular damage caused by segments of dead worms²⁶, reduced the extent and severity of myointimal proliferation caused by implanted living worms²⁷, and improved pulmonary parenchymal disease and

intimal proliferation in dogs receiving thiacetarsamide after previous living HW implantation.²⁴ More recent studies, however, have produced controversial results. Aspirin administered to dogs with implanted HW, receiving adulticide, showed no improvement in pulmonary angiographic lesions and had more severe tortuosity than did controls and dogs receiving heparin.²⁸ The authors emphasized that the ideal aspirin dosage would inhibit platelet function, but not PGI₂ production. Dillon and associates demonstrated that the aspirin dosage required to decrease platelet reactivity by at least 50% was increased by nearly 70% with HWI (implantation model) and by nearly 200% with a model (dead worm implantation) of PTE.²⁹ There were not significant differences in severity of pulmonary vascular lesions in aspirin-treated vs control dogs. For these reasons, the American Heartworm Society does not endorse antithrombotic therapy for routine treatment of HWD.^{5,5a}

As mentioned above, aggressive macrolide therapy (ivermectin, given at 6 ug/kg weekly instead of monthly), coupled with a complex regimen of doxycycline (10 mg/kg/day) hastens worm destruction and quickly eradicates microfilariae. This has resulted in increasing use of doxycycline in the management of HWI in dogs.

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

Microfilaricidal therapy. Despite the fact that no agent is FDA-approved for the elimination of microfilaria, microfilaricidal therapy is traditionally instituted 4-6 weeks after adulticide administration. The macrolides offer a new and effective alternative to levamisole and dithiazanine.^{5,5a} Microfilariae are efficiently and rapidly cleared with ivermectin at 50 ug/kg (approximately 8 times preventative dose) or milbemycin at 500 mg/kg (preventative dose), although this represents an extra-label use of these drugs.^{5,5a} The off-label use of livestock formulations of ivermectin is discouraged because of the possibility of dosing errors and resultant toxicity. Adverse reactions, the severity of which is likely related to microfilarial numbers, were observed in 6% of 126 dogs receiving ivermectin at the microfilaricidal dose (50 ug/kg).³⁰ Signs included shock, depression, hypothermia, and vomiting. With fluid and corticosteroid (dexamethasone at 2-4 mg/kg IV) therapy, all dogs recovered within 12 hours. One fatality was observed 4 days after microfilaricidal therapy. Similar findings and frequency have been reported with milbemycin at the preventative dosage.³¹ Dogs so treated should be hospitalized and carefully observed for the day. Dogs <16 kg, harboring >10,000 microfilaria per ml blood, are more apt to suffer adverse reactions.³² Benadryl (2 mg/kg IM) and dexamethasone (0.25 mg/kg IV) can be administered prophylactically to prevent adverse reactions to microfilaricidal doses of macrolides.

A 90% microfilaricidal success rate can be expected with ivermectin²⁵, while milbemycin at 500 mcg/kg cleared 6/8 (75%) dogs which had received adulticide therapy and did not harbor male and female adults; microfilarial numbers were reduced by 99% on the day after treatment.³¹ A slower microfilarial kill rate can also be achieved with ivermectin, moxidectin, moxidectin-imidacloprid, and selamectin at preventative doses.¹⁻⁴

The time-honored approach to ridding the patient of microfilariae involves macrolide therapy (50 mcg/kg for ivermectin or 500 mcg/kg milbemycin) instituted 3-6 weeks after adulticide.^{5,5a} In 2-3 weeks, a second microfilaria concentration test is performed and, if negative, preventative started. If still positive, the treatment is repeated or alternatively, chemoprophylaxis begun (assuming that no adverse reaction occurred on the initial treatment).^{5,5a} Persistent antigenemia (after 6-7 months) indicates continued patent infection.

This author chooses an alternative approach (Figure 1), beginning the administration of a macrolide preventative at the time of diagnosis, often days to weeks prior to adulticidal therapy. With the "slow microfilaricides" (ivermectin, moxidectin, or selamectin), there is little chance of an adverse reaction, but the owner is warned and advised to administer the medication on a day when he/she will be at home. If Milbemycin (a superior microfilarial agent) is used, it is administered in the hospital and/or preceded by administration of dexamethasone and benadryl, as described above. If this approach is used, the dog must be rendered microfilariae-free by 1-3 months post-diagnosis. Recent evidence demonstrates that concurrent usage of a macrolide and doxycycline reduces microfilarial numbers more rapidly, rendering dogs negative in less than 3 months. It is imperative that dogs on macrocyclic lactones be rendered microfilaria-free.

DRUG	Heartworms	Roundworms	Hookworms	Whipworms	Ticks	Fleas	Mites
Iver/Pyrantel*	+	+	+				
Milbe-Lufen [#]	+	+	+	+			
Milbe-Spino ^κ	+	+	+	+		+	
Moxi Inject [♦]	+		+				
Moxi-Imida [❖]	+	+	+	+		+	
Selamectin [●]	+				+	+	+

Table 1. Comparison of spectra of 6 heartworm preventive macrocyclic lactones or macrocyclic lactone combinations, in alphabetical order. * = Heartgard^R Plus, Iverhart^R Plus, Triheart^R Plus; combinations of ivermectin and pyrantel pamoate; ivermectin, pyrantel pamoate and praziquantel (Iverhart^R Max) also has a label claim for tape worms. # = Sentinal^R; Milbemycin-oxime and lufenuron. κ = Trifexis^R; milbemycine-oxime and spinosad. ♦ = Proheart^R 6; long-acting injectable moxidectin. ❖ = Advantage Plus^R; moxidectin and imidacloprid topical. ● = Revolution^R; selamectin topical; mite efficacy includes ear mites and sarcoptic mange.

Figure 1. The author's preferred approach to adulticidal therapy in virtually *all* (severely affected or not) dogs infected with heartworms includes 3 doses of melarsomine. Macrolide prophylaxis is begun at the time of diagnosis, if not already in use. *If microfilaremic, care should be taken to prevent or observe and treat adverse reactions, based on microfilarial numbers and macrolide used. It is imperative to rid patients receiving macrolides of microfilariae to reduce the chances of resistance.

