Proceedings of the
World Small Animal Veterinary Association
Mexico City, Mexico – 2005

Hosted by:

Reprinted in the IVIS website with the permission of the WSAVA
HEARTWORM DISEASE IN DOGS: AN UPDATE

Clarke Atkins, DVM
Diplomate, ACVIM (Internal Medicine & Cardiology)
North Carolina State University, Raleigh, NC

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 macrodilides 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.

In the past, ELISA tests measured antibody concentrations but the sensitivity and specificity was not adequate to allow their recommendation for routine screening. This lack of specificity increases the number of false positives to an unacceptable level when used in areas with low incidence or to screen dogs receiving preventative. Today's commercial antigen tests (ELISA and immunochromatographic) measure heartworm antigen and have achieved virtually 100% specificity, making them the screening tests of choice. Sensitivity is also excellent, overall greater than 85%. This compares favorably with the concentration tests which may yield 5-67% (typically 10-25%) false negatives, depending on the geographic area in question. Direct smear tests are generally 5-10% less accurate. 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 <10% were negative when 3-5 worms were present, and no false negatives resulted when >20 worms were present. False negative tests also result from all-male infections, because these tests detect antigens produced by gravid females. 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. 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. The ELISA antigen technology also allows semi-quantitation of worm burden and efficacy of adulticide therapy 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. 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.

As suggested above, macrolide preventative therapy typically results in clearance of microfilaria within 6-8 months of therapy. In addition, embryostasis may be permanent. Thus, the use of direct smears, the modified Knott test, and filter tests for screening test in 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. Most authors, however, have disagreed with this stance and recently the Companion Animal Parasite Council has made a formal recommendation for yearly testing. Nevertheless, the only effective testing modality in the ever-increasing percentage of dogs receiving monthly preventative is the antigen test.
Other alternative or supplementary diagnostic tests include thoracic radiographs which are an excellent, though expensive means of diagnosing heartworm disease (HWI), but not simple HWI. 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. 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 is not consistent (low sensitivity). In caval syndrome, however, the appearance is consistent and characteristic. 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. Nonselective angiography can be utilized to prove the presence of non-caval syndrome HWI when all else fails.

It has been recommended that dogs previously untested and old enough to harbor adult HW (6 months), be tested with both ELISA and microfilaria tests prior to being placed on preventative. This is because, even though the antigen test is the more sensitive, up to 1% of antigen-negative dogs may harbor microfilaria. Microfilaricidal doses of ivermectin, so misdiagnosed, might then suffer severe, even fatal reactions, if placed on diethylcarbamazine (DEC) preventative. This approach may be overly conservative, especially in dogs placed on monthly preventative which is less likely to produce a serious adverse reaction in a microfilaremic dog than is DEC. In addition, if one assumes a 10% prevalence in the population, and an 85% ELISA antigen test sensitivity, the above-mentioned 1% occurrence would be realized approximately once in every 10,000 unprotected dogs tested and treated with DEC.11

Dogs in cold climates and on DEC are traditionally tested with microfilaria tests before reinstituting DEC each Spring. Antigen testing is preferable because of superior sensitivity and because they can be used alone or to supplement microfilarial testing if there are questions about the DEC compliance. If yearly testing is performed in dogs receiving macrolide therapy, the ELISA antigen tests are mandatory as infections in such dogs are occult. This is true even in cold climates after intentional interruption of preventative therapy because there is infrequent recrudescence of microfilaria with the macrofilaricatives. In dogs showing signs of HWD, an antigen test is performed first because of the superior sensitivity. If positive, a microfilarial test is performed to determine if microfilariae (and with them the increased risk of preventative administration) are present. Other tests, as described above, can be employed if the diagnosis is still not forthcoming.

Prevention

The introduction of the macrolide agents ivermectin (Heartgard®), milbemycin oxime (Interceptor®), moxidectin (ProHeart® and ProHeart® 6 [recently voluntarily removed from U.S. market]) and selamectin (Revolution™) has provided the veterinary profession with effective heartworm (HW) preventative in a variety of formulations. Such agents, because they interrupt larval development during the first 2 months after infection, have a large window of efficacy and are administered monthly or less frequently. These agents are superior to diethylcarbamazine (DEC) in: convenience; producing less severe reactions when inadvertently given to microfilaremic dogs; allowing a grace period for inadvertent lapses in administration; efficacy with treatment lapses of up to 2-3 months when used continuously for the next 12 months; and lastly, having a dual role as microfiliaricides.2-4

Ivermectin, a chemical derivative of avermectin B1 which is obtained from Streptomyces sp. is effective against a range of endo- and ectoparasites and is marketed as a once monthly heartworm preventative. It is also marketed in a form with pyrantel pamoate to improve efficacy against intestinal parasites (Table 1). Macrolides provide a wide window of efficacy and provide some protection when lapses in therapy. Ivermectin is effective as a prophylactic with lapses of up to 2 months occur. This is extended with continuous 12 month administration post-exposure to 3 months with 98% efficacy and to 4 months with 95% efficacy.1 As stated above, ivermectin is microfilaricidal at preventative doses (6-12 mcg/kg/month), resulting in a gradual decline in microfilarial numbers. Despite this gradual microfilarial destruction, generally mild, adverse reactions (transient diarrhea) can occur if administered to microfilaricidal dogs.5,5a Collies have been identified as a breed in which certain individuals are at increased risk of central nervous system signs and even death due to increased concentrations of ivermectin in the central nervous system. It is important to note that such adverse reactions have not been identified at preventative or even microfilaricidal doses of ivermectin. When used appropriately, ivermectin is virtually 100% effective in preventing HWI. Additionally, recent studies have shown ivermectin to have partial adulticidal properties when used continuously for 16 months6,20 and 100% adulticidal efficacy if administered continuously for over 30 months20 in experimental infections.

Milbemycin oxime is a member of a family of milbemycin macrolide antibiotics derived from a species of Streptomyces. At 500-999 ug/kg, it has efficacy against developing filarial larvae,
arresting development in the first 6 weeks. It can therefore be given at monthly intervals with a “reachback effect” of 2 months when doses are inadvertently delayed. With 12 months= continuous treatment post-exposure, this Asafety net@ can be extended to 3 months with 97% efficacy, falling to 41% with lapses of 4 months.1 At the preventative dosage, milbemycin is a broad-spectrum parasiticide, being also effective against certain hookworms, roundworms, and whipworms. In microfilaremic dogs, milbemycin has greater potential for adverse reactions than do other macrolides, as it is a potent microfilaricide at preventative doses.2 Adverse reactions, similar to those observed with ivermectin at microfilaricidal doses may be observed in microfilaremic dogs receiving milbemycin at preventative doses.7 As with microfilaricidal dosages (50 ug/kg) of ivermectin, benadryl (2 mg/kg IM) and dexamethasone (0.25 mg/kg IV) may be administered prior to milbemycin to prevent adverse reactions, particularly in dogs with high microfilarial counts. Milbemycin is also safe for use in collies at the preventative dose. With appropriate use, milbemycin is virtually 100% efficacious as a HW prophylactic.

The macrolide preventative, moxidectin, has more recently been marketed and has been shown to be safe and virtually 100% effective at 3 mcg/kg given monthly or bimonthly up to 2 months post-infection.8 Moxidectin, at this dosage, is gradually microfilaricidal and did not produce adverse reactions in a small number of microfilaremic dogs treated with the prophylactic dose.9 At 15 mcg/kg, 98% reduction in microfilarial numbers was documented 2 months post-treatment.9 Lastly, moxidectin appears to be safe in collies.10 A new liposomal formulation of moxidectin gives 6 months’ protection with one subcutaneous injection.11 With 12 months’ (2 injections) continuous treatment, injectable moxidectin is 97% effective at preventing infection after a 4 month lapse in preventative therapy.12 Label claims suggest that this drug should not be administered to dogs known to have adult heartworm infections. In September, 2004, the latter product has been voluntarily removed from the U.S. market, but still remains available in other countries.

Most recently, a semi-synthetic macrolide, selamectin, has been developed and marketed. It is unique in its spectrum and in the fact that is applied topically once monthly. Its efficacy is similar to that of other macrolides (virtually 100%, when used as directed).13,14 At 6-12 mg/kg topically, this preventative is effective at preventing heartworms infection and kills fleas and flea eggs, sarcoptic mange mites, ticks and ear mites.13 Bathing and swimming, as soon as 2 hours after application, did not affect efficacy. Safety has been shown at 10-fold topical doses, with oral consumption of single doses, and, in ivermectin-sensitive collies, at recommended dosages and five-fold overdoses for 3 months.15 Like other macrolides, selamectin has at least a 2 month reachback effect and with 12 months’ continuous administration, is 99% protective after 3 month lapses in prophylaxis.13,16 Selamectin has microfilaricidal acivity similar to other macrolides.16

In summary, the macrolides offer a convenient, effective and safe method of HW prophylaxis with varying spectra and methods of administration (Table 1). Prophylaxis should be commenced at 6-8 weeks of age in endemic areas, or as soon thereafter as climatic conditions and label instructions dictate.5,5a Although safer than DEC in microfilaremic dogs, before first time administration, any dog over 6 months of age and at risk of infection, should be tested (antigen test, followed by a microfilaria test, if positive). Although protective for at least 8 weeks post-exposure, macrolides should be administered precisely as indicated by the manufacturer and this author prescribes prophylaxis year-round. This recommendation has now been made formally by the Companion Animal Parasite Council.7a If accidental lapses occur, the preventative should be reinstituted at recommended doses and maintained for a continuous 12 months (or continuously). Macrolides can also be used to “rescue” dogs which have lapsed in their DEC daily therapy for up to 60-90 days.5,5a If a lapse in preventative is prolonged (>2 months) and the risk for HWI deemed moderate or high, macrolides should be continued for a year without interruption. In addition, an antigen test should be performed approximately 6 months after the last chance for exposure to detect infection.

**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 thiacectarsemide.17 This product, which is administered twice, at 2.5 mg/kg q24h, has a mean retention time 5 times longer than thiacectarsemide 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 thiacectarsemide.18 With 2 doses, the efficacy is over 96% with the useful flexibility of a 50% worm kill with 1 dose. A “split-dose” protocol can be utilized in severely afflicted individuals or in those in which pulmonary thromboembolism (PTE). 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 all cases unless there is financial constrain or underlying concern for arsenical toxicity (for example, preexistent severe renal or hepatic disease). 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. 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. 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) can be given at the time melarsomine is administered to lessen the reaction.

It is now known that certain macrolides have adulticidal properties. Ivermectin, when administered for 31 months continuously has nearly 100% efficacy in young heartworm infections. 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. Selamectin, when administered continously for 18 months killed approximately 40% of transplanted worms. Sustained release moxidectin also appears to have some adulticidal efficacy. While there may be a role for this therapeutic strategy 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.

Surgical removal of HW can minimize PTE, as compared to pharmacologic adulticides, such as melarsomine. 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. For allergic pneumonitis, prednisolone (1 mg/kg/day) is administered for 3-5 days and discontinued or tapered, as indicated. The response is generally favorable. Prednisolone has also been advocated for the management of PTE. Because of the potential for fluid retention, steroids should be used cautiously in the face of heart failure.

Antithrombotic agents have received a good deal of attention in the management of HWD. Potential benefits include reduction in severity of vascular lesions of HWD, reduction in pulmonary arterial vasoconstriction and pulmonary hypertension, as well as minimization of post-adulticidal PTE. Aspirin has shown success in diminishing the vascular damage caused by segments of dead worms, reduced the extent and severity of myointimal proliferation caused by implanted living worms, and improved pulmonary parenchymal disease and intimal proliferation in dogs receiving thiacetarsemide after previous living HW implantation. More recent studies, however, have produced controversial results. Aspirin administered to dogs with implanted HW, receiving adulticide, showed no improvement in pulmonary angiographic lesions and had more severe tortuosity than did controls and dogs receiving heparin. These 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. There were not significant differences in severity of pulmonary vascular lesions in aspirin-treated vs control dogs. For these reasons, the American Heartworm Society does not endorse antithrombotic therapy for routine treatment of HWD.

Cage rest is an important aspect of the management of HWD after adulticidal therapy, after PTE, or during therapy of heart failure. This can often be best, or only, accomplished in the
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 macrodiles offer a new and effective alternative to levamisole and dithiazanine. 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. The off-label use of livestock formulations of ivermectin is discouraged. 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. Signs included shock, depression, hypothermia, and vomiting. With fluid and corticosteroid (dexamethasone at 2-4 mg/kg IV) therapy, all dogs recovered within 12 hours. One fatality was observed 4 days after microfilaricidal therapy. Similar findings and frequency have been reported with milbemycin at the preventative dosage. Dogs so treated should be hospitalized and carefully observed for the day. Dogs <16 kg, harboring >10,000 microfilaria per ml blood, are more apt to suffer adverse reactions. Benadryl (2 mg/kg IM) and dexamethasone (0.25 mg/kg IV) can be administered prophylactically to prevent adverse reactions to microfilaricidal doses of macrodiles.

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

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. 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). Persistent antigenemia 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 is used, it is administered in the hospital and/or preceded by administration of dexamethasone and benadryl, as described above.
**Comparison of Macrolides in Dogs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>HW</th>
<th>Mf</th>
<th>Adulticidal</th>
<th>Hook</th>
<th>Whip</th>
<th>Round</th>
<th>Tape</th>
<th>Flea/eggs</th>
<th>Tick</th>
<th>Sarcoptes</th>
<th>Ear</th>
<th>Mites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Milbemycin</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Moxidectin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Selamectin</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* ivermectin/pyrantel pamoate  
** milbemycin/lufenuron  
***injectable formulation

**Table 1.** Comparison clinical spectrum of commercially available macrolides. () = partially effective or incompletely studied. Chew = chewable, Tab = flavored tablet, Tab/I = tablet or injectable, Top = topical.
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. See text for complete description.
References: Diagnosis


References: Prevention and Treatment


ivermectin or milbemycin starting at various intervals after Dirofilaria immitis infection. Vet Ther 2001; 2:193-207.


