WHAT’S NEW, DIFFERENT AND IMPORTANT IN HEARTWORM DISEASE IN 2017?
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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. 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. 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, 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® Plus, Iverhart® Plus, TriHeart® Plus), ivermectin with pyrantel pamoate (Heartgard® Plus, Iverhart Plus®, TriHeart® Plus), ivermectin with pyranl pamoate and praziquantel (Iverhart Max®), milbemycin oxime (Interceptor®), milbemycin with lufenuron (Sentinel®) and with spinosad (Trifexis®), selamectin (Revolution®), and moxidectin (ProHeart®, ProHeart® 6), and moxidectin with imidocloprid (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. 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. 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. In the event of a lapse in preventative administration during a time of known exposure risk, an antigen 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. Some but not all macrolides have adulticidal activity if used continuously for prolonged periods.

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 (excerpt):

“...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 microfilaria 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.” 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 (i.e., 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 microfilariae are eradicated in the first months of macrocyclic 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.

**Blocking Agents: Repellent Insecticides.** Permethrin, a third-generation pyrethroid, is an insecticide which has a rapid knockdown effect against a variety of species. This molecule is currently found in a topical form in at least 2 repellents that have utility against mosquitoes and, thereby, heartworms. One has been shown to provide month-long repellence and lethality to 3 heartworm vectors (*A. aegypti* and *albopictus* and *C. pipiens*). The second has been shown to repel and kill *A. aegypti* mosquitoes allowed to feed on dogs infected with JYD-34 HW strain. Feedings on untreated control dogs yielded “80-95% engorgement rate, with 95% of mosquitoes harbouring L1. However, only 2% of mosquitoes became engorged on treated dogs 28 days after the medication was applied. The implication from these studies is that a monthly application of permethrin repels and kills mosquitoes, effectively eliminating HW transfer to and from the feeding victims, and also reducing the discomfort of mosquito bites and local mosquito populations. This approach is also effective for protecting against ML-resistant HW and promises to be an effective adjunct to current preventive measures.

**THERAPY**

**Doxycycline and Wolbachia.** The benefits of doxycycline result from its ability to remove or reduce the burden of *Wolbachia*, a rickettsial organism that exists in a symbiotic relationship with heartworms (and other filarids), occupying the reproductive tract and lateral chords of the host parasite (Figure 2). *Wolbachia* are necessary for the parasite (in this case, *Dirofilaria immitis*) to develop, thrive, reproduce, and maintain infectivity.

Doxycycline has been used to (presumably) rid the parasite of *Wolbachia* organisms; therefore, *D. immitis* organisms do not thrive, may deteriorate and die, and have reduced reproductive potential, which helps manage HWD in infected dogs and reduces potential for infection in other dogs. There has been concern raised as to the potential for resistance of bacteria to doxycycline being developed if it is used in all cases. This, in my opinion, is worth considering as doxycycline is widely used and valuable to our profession (and physicians) in the treatment of a variety of infectious processes. On the other hand, it is widely used for other disease and the concerns for resistance generally occur when drugs are used at sub-optimal dosages and durations of therapy. Neither of these will result from the current recommendations for HWD.

Potential and realized benefits derived from anti-*Wolbachia* therapy include:

1. **Reduce Ability of Parasite to Reproduce**
   - It has been shown that the *Wolbachia* organism is suppressed (killed) by doxycycline and the resulting, negative effects on the heartworm reproductive system renders the parasite infertile or less fertile (temporarily?), with reduced microfilarial numbers.\(^{1,2,3}\)

2. **Reduce Infectivity**
   - In doxycycline-treated dogs, even if microfilariae are produced and ingested in a mosquito’s blood meal, the resultant L3 are incapable of producing infection, reducing the spread of HWD.\(^{1,2,3}\)

3. **Potentiate Adulticidal Therapy and/or Enhance of Slow- or Soft-kill Efficacy**
   - Most agree that *Wolbachia* is an obligate symbiont for *D. immitis*, which makes us hope that *Wolbachia* eradication with antibiotics would result in the nematode’s demise. Unfortunately, prolonged doxycycline therapy does not kill heartworms because they are not sufficiently bound to their bacterial symbionts.\(^{4}\) However, two studies\(^{5,6}\) have demonstrated that doxycycline shortens the time until worm death when administered chronically
with ivermectin/pyrantel at preventive dosages but with a decreased dosing interval:

Study 1: Using surgically transplanted worms, it was shown that a combination of:

- Weekly ivermectin (at the monthly preventive dosage of 6 mcg/kg) and
- Daily doxycycline (10 mg/kg Q 24 H for 24 weeks of a 36-week study)
  reduced heartworm burden by 78% after 9 months of therapy as compared to control dogs.³

Study 2: Using echocardiography, this study evaluated the effect of:

- Doxycycline (10 mg/kg Q 24 H for 30 days) and
- Ivermectin/pyrantel (6–14 mcg/kg every 15 days for 180 days; then monthly)
  on microfilariaemia, heartworm antigenemia, and parasite load. In naturally-infected dogs from an endemic
  region of Italy, all became negative for circulating microfilariae by day 90 and 73% became antigen negative by
day 300.⁵

The results of these studies suggest that the combination of doxycycline and ivermectin is (slowly) adulticidal in
dogs with D. immitis, which indicates that doxycycline enhances therapy for a soft- or slow-kill method.

4. Reduce Microfilarial Burdens More Effectively, Safely, & Rapidly
In the transplanted worm model mentioned in Study 1, it was shown that a combination of weekly ivermectin (6 mcg/kg) and daily doxycycline (10 mg/kg Q 24 H) eliminated microfilariae over 8 to 12 weeks.³

This elimination is relatively fast, but not so quick that therapy results in the adverse, shock-like reactions seen with rapid destruction of large numbers of microfilariae. In addition, subacute removal of microfilariae lessens the chance of macrocyclic lactone resistance, especially when the practitioner is forced to use the slow-kill method due to owner finances or unavailability of adulticide (ie, melarsomine).

5. Reduce Lung Reaction to Worm Death (Spontaneous & Post-adulticide)
Study 1 also showed that the combination of weekly ivermectin (6 mcg/kg) and daily doxycycline (10 mg/kg Q 24 H) significantly reduced lung lesions after melarsomine therapy.³⁶

6. Kill Developing Larvae
Recently, McCall, et al, demonstrated that, while doxycycline (even with ivermectin) does not have rapid adulticidal efficacy, doxycycline monotherapy does stop the progression of infective larvae to adulthood when administered for the first 30 days of infection at 10 mg/kg Q 24 H.⁷

- If the 30 days of administration begin on day 40 of infection, however, the effect is partially lost, with 2% of L3 reaching adulthood.
- If the larvae reach 65 days before doxycycline is begun, only 52% reach adulthood.⁷

Therefore, in addition to reducing adverse effects from heartworm death, doxycycline begun on the day of diagnosis will help close the potential seasonal window of continuous infection, which means that, during certain times of year when exposure is continuous (warmest months), the host may have developing larvae of all stages. However, younger—tissue-stage larvae become less vulnerable with development, maturing to a point where (1) macrocyclic lactone therapy is ineffective and (2) they are too young for elimination with melarsomine. This treatment failure, potentially alleviated with pre-adulticide doxycycline, can result in the perception of product failure (preventive or adulticide).

Currently the best data we have argues that the dosage, if tolerated, is 10 mg/kg Q 12 H for 30 days, administered prior to adulticidal therapy (Figure 2). If this dose is not tolerated, it can be reduced to 5 mg/kg Q 12 H.⁷ I advocate a second month’s delay in adulticidal therapy to allow the parasite to deteriorate maximally and, thereby, further reduce the pulmonary reaction to worm death. Benefits include:

- Prevention of maturation of recently acquired infection (tissue phases)
- Reduced pulmonary reaction to dying worms
- More rapid and complete eradication of microfilariae (potentially reducing risk of heartworm resistance to macrocyclic lactones)
- Enhancement of vermicidal efficacy of ivermectin if using slow-kill method.

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 thiacetarsamide and its metabolites are free in the
plasma, on which HW feed.\textsuperscript{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 thiacetarsamide, the agent previously used.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{6,16,20} Ivermectin, when administered for 31 months continuously has nearly 100\% efficacy in young heartworm infections.\textsuperscript{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.\textsuperscript{21} Selamectin, when administered continuously for 18 months killed approximately 40\% of transplanted worms.\textsuperscript{16} Sustained release moxidectin also appears to have some adulticidal efficacy.\textsuperscript{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.\textsuperscript{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, with a current protocol calling for ivermectin at preventive dosages given monthly (some advocate administering it every 2 weeks for the first 6 months), coupled with doxycycline for 30 days at 10 mg/kg/day. The American Heartworm Society advocates, when melarsomine is unavailable, to use doxycycline at this dosage one month on, two months off, etc, until the patient reverts to an antigen-negative status, while the author uses doxycycline for only 1 month. 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.\textsuperscript{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.** 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.\textsuperscript{5,54} Microfilariae are efficiently and rapidly cleared with ivermectin at 50
ug/kg (approximately 8 times preventative dose) or milbemycin at 500 u g/kg (preventative dose), although this represents an extra-label use of these drugs. 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). 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 macrolides.

A 90% microfilaricidal success rate can be expected with ivermectin, 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 after treatment. A slower microfilarial kill rate can also be achieved with ivermectin, moxidectin, moxidectin-imidacloprid (recently approved by the FDA as a microfilaricide), 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 (after 6-7 months) indicates continued patent infection.

This author chooses an alternative approach (Figure 1a), 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.

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 microfilaricidal, 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 chance of resistance.
HWI

Macrolide @ preventative dosage monthly

2 Months

Doxycycline x 4 wks

Reduced Activity

If Mf+, render Mf-free

Immiticide
2.5 mg/kg +/- NSAID

-1 Month (1 – 3 months)

Immiticide 2.5 mg/kg twice @ 24hr interval +/- NSAID

1 Month’s Cage Rest

1 Month’s Cage Rest

Modified from Atkins, Miller Vet Med 2003