

Canine Heartworm Update: What we forgot, what we thought we knew and what we really need to know.

**Michael W Dryden DVM, MS, PhD, DACVM (parasitology)
Department of Diagnostic Medicine/Pathobiology
Kansas State University, Manhattan KS**

Hosts and geographic distribution

- Dogs, coyotes, cats, ferrets, fox, etc.
- U.S. reported in all 50 states (endemic at least regionally in all states but Alaska)
- In a national survey veterinarians in the United States reported over 255,000 dogs diagnosed with heartworm infection in 2004. In the aftermath of the 2005 hurricane season >11,000 rescued animals were collected at animal shelters; these animals were transported to at least 37 states. In one study of over 3,000 dogs and cats, 48.8% of dogs and 4.0% of cats relocated were heartworm positive.¹

Life Cycle

Adults occur naturally in pulmonary arteries and occasionally the right heart; occasionally aberrant migrations occur to other locations in the body. (Showing adult worms in right ventricle of a dog's heart to a client may be an effective tool but it is typically a post-mortem finding)

1. Female *D. immitis* in pulmonary arteries and right heart produce microfilariae that enter the circulation.
2. Microfilariae may survive up to 3.5 years in the vascular system.
3. Mosquitoes become infected by feeding on infected dogs and ingesting microfilariae.²
 - 25 species of mosquitoes have been found naturally infected in the United States.
4. Microfilariae exit midgut and migrate to the malpighian tubules & undergo morphologic change to L1, then develop from the L1 – L2.³
5. L2 migrate into hemocoel and move towards the head of the mosquito.
6. L2 molt to L3 infective larvae in the salivary glands of the mosquito.
7. L3 exhibit positive thermotaxis, and when the mosquito (I.H.) bites a dog (or other host) the infective L3 exit the labium in a drop of hemolymph and fall around the bite wound.³

- Typically have 2 to 3 L3, but numbers as high as 30 have been recorded. Great variability.³
- 8. L3 migrate into bite wound and then reside in SubQ and molt to the L4 in subcutaneous tissues within 3 – 12 days.
- 9. L4 migrate to SubQ or muscle in thorax and molt to the immature adult, 50 – 70 days.⁴
- 10. Immature adults begin migration to pulmonary arteries (rarely heart) by 70 – 90 days P.I.; by day 120 virtually all worms are in pulmonary vasculature.
- 11. 2-4 cm long
- 12. *D. immitis* mature and then male and female *D. immitis* mate and females begin depositing microfilariae (L1) within 6 – 7 months P.I.
- 13. In dogs adult *D. immitis* may live 5 – 7 years
- 14. Despite popular misconception, adult heartworms rarely inhabit the heart. Rather they inhabit the pulmonary arteries. In heavy infections, if the cardiac output falls, or death occurs, they may drift (“migrate retrograde”) to the heart.

Diagnosis

Historically diagnosis was made by recovering and identifying the microfilariae. However, diagnostic procedures have changed due to increased use of macrolide preventives which may suppress microfilariae populations, the presence of occult (amicrofilaremic dogs) infections and the improved sensitivity and specificity of immunodiagnostic tests. Most antigen tests are highly sensitive (1+ female worms) and highly specific (rare cross reactions with other antigens).⁵⁻⁷ ELISA, immunochromatographic and hemagglutination antigen test systems are available for detecting circulating heartworm antigen produced by mature female worms (uterine antigen). Approximately 10% of dogs are antigen positive 5 months post-infection, but it is not until 7 months that >95% are antigen positive. Depending on the sensitivity of the particular heartworm antigen test, antigenemia may proceed, but sometimes lags the appearance of microfilariae, by a few weeks. In addition, antigen tests may remain positive 4 – 6 months following death of adult *D. immitis*. In general the antigen tests will detect 1 female worm 62 – 64% of the time or two female worms 82 – 88% of the time (sensitivity).^{5,6} Infections with 1 - 4 female worms 93 -100% depending upon the specific test.⁵⁻⁷ Tests for microfilariae are used to recover *D. immitis* microfilariae from blood. Blood should be drawn in the afternoon due to nocturnal periodicity of microfilariae.

Recently several articles have demonstrated that antigen tests may not test positive in some dogs and cats.⁸⁻¹¹ It appears that antigen-antibody complexes are formed that bind the heartworm antigen so that it is “unavailable” to react on the available antigen

tests.⁸⁻¹⁰ These complexes can be overcome by heat-treatment of serum samples to denature the complex. Serum samples are heated to 103°C for 10 minutes in a dry heat-block and then spun in an ultracentrifuge to separate serum from coagulum left after heating. This heated serum is then used in the antigen tests. This is not a diagnostic approach easily achieved in many veterinary practices. Heating of serum is not approved for any current heartworm antigen test and heating of serum will destroy any antibodies in the sample if testing for tick transmitted diseases is warranted. Heating of samples may be considered if 1) a dog with clinical signs of heartworm diseases tests both antigen and microfilariae negative, 2) if discrepant results are found on different antigen tests, 3) at 6 months post-adulticide therapy and 4) if monitoring dogs on “slow-kill” therapy. It has been found that upwards of 50% of dogs on slow-kill therapy that have become antigen negative may in fact still have adult heartworms.¹¹

Treatment

Treatment (only adulticide currently on the market is melarsomine (Immiticide®; Merial)

- Deep intramuscular injection into the epaxial musculature with a fresh 1.5" needle, restrict activities (cage rest) for 4 – 6 weeks after treatment. Activity against mature *D. immitis*. Adult males more susceptible than female *D. immitis*. Melarsomine (3 dosage regimens are FDA approved; 2 are commonly used). One 2.5 mg/kg IM (deep muscular injection) dose followed 30 days later by two IM doses over 24 hr appears to be the safest dosage regimen and is very effective. AHS recommends this treatment approach. (Efficacy 98.7%; 100% males 98% females)
- Dead worms being swept to the lungs can be a consequence of successful adulticide therapy and reactions may be severe or even life threatening if infection is heavy or pulmonary arterial disease is extensive. Reaction in the lungs is often an intensive immune response to the dead worms. If signs of embolism (low grade fever, cough, hemoptysis, exacerbation of right heart failure) develop, they are usually evident within 7 to 10 days, but occasionally as late as four weeks after completion of adulticide administration. A pivotal factor in reducing the risk of embolic complications is exercise restriction during the critical month following treatment.
- No exercise or stress should be allowed for 4 – 6 weeks post treatment.

The relationship of heartworm, *Wolbachia* and doxycycline

Wolbachia pipientis a symbiotic gram negative intracellular bacteria that is closely related to rickettsia. It has been identified in human and animal filarial nematodes. All *D. immitis* parasites harbor *Wolbachia*. *Wolbachia* organisms are maternally transferred from one filarial generation to the next. Bacteria are present in all

life stages of the parasite. *Wolbachia* are released in large numbers at the death of the parasite and during production and release of microfilariae.¹²

Generally filariae free of *Wolbachia* after treatment with tetracyclines show inhibition of maturation, survival and reproduction. It has been shown that a combination of doxycycline/macrocyclic lactones is microfilaricidal and adulticidal.¹²⁻¹⁶

American Heartworm Society Treatment Guidelines (July 2014)

(extracted from Table 1 Canine Guidelines: <https://www.heartwormsociety.org>)

	<ul style="list-style-type: none"> ▪ Treatment
<ul style="list-style-type: none"> ▪ Day 0 	<ul style="list-style-type: none"> ▪ Dog diagnosed and verified as heartworm positive. ▪ Positive Ag test verified with 2nd Ag or microfilaria (MF) test ▪ Clinical signs with one positive Ag test and MF test (for status) ▪ Begin exercise restriction. ▪ The more pronounced the symptoms, the stricter the exercise restriction. ▪ If the dog is symptomatic: ▪ 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 week
<ul style="list-style-type: none"> ▪ Day 1 	<ul style="list-style-type: none"> ▪ Administer heartworm preventive. ▪ If microfilariae are present, pretreat with antihistamine and glucocorticosteroid to reduce risk of anaphylaxis. ▪ Observe for at least 8 hours for signs of reaction.
<ul style="list-style-type: none"> ▪ Day 1-28 	<ul style="list-style-type: none"> ▪ Doxycycline 10 mg/kg BID for 4 weeks ▪ Reduces pathology associated with dead heartworms ▪ Disrupts heartworm transmission

▪ Day 30	▪ Administer heartworm preventive.
▪ Day 60	▪ Administer heartworm preventive. 1st melarsomine injection 2.5 mg/kg intramuscularly (IM) ▪ Rx prednisone 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg EOD 3rd and 4th week ▪ Cage restriction/on leash when using yard
▪ Day 90	▪ Administer heartworm preventive. 2nd melarsomine injection 2.5 mg/kg IM
▪ Day 91	▪ 3rd melarsomine injection 2.5 mg/kg IM ▪ Rx prednisone 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg EOD 3rd and 4th week ▪ Continue exercise restriction for 6 to 8 weeks
▪ Day 120	▪ Test for presence of microfilariae. ▪ Establish year-round heartworm prevention.
▪ Day 271	▪ Antigen test 6 months after completion.

Prevention (Chemoprophylaxis) - Dogs

- Heartworm preventives are the macrocyclic lactones (ivermectin, milbemycin oxime, moxidectin and selamectin). These drugs have exceptional anthelmintic activity against L₃ and L₄. The “preventive” effect of the **monthly** formulations is achieved by killing L₃ and L₄ once a month when the products are administered. With monthly products dogs are essentially “dewormed once a month” for subcutaneous nematode heartworm larvae. Monthly administration essentially “reaches back” in time 30 days killing all deposited L₃ and molted L₄ with the short term “pulse” (effective blood levels only last a few days) of the macrocyclic lactone anthelmintics.

Reports of Lack of Efficacy of Preventives (Resistance?)

Reports of lack-of-efficacy have occurred at an increased rate from the lower Mississippi delta region. Reasons are multi-factorial and not clearly understood. Recent data generated in studies using a *D. immitis* strain called MP3 (collected in Georgia) have indicated that the MP3 strain is more susceptible to moxidectin than to other preventives as it was 100% at a single dose.¹⁷ Ivermectin, milbemycin oxime and selamectin preventives were 95% - 99% effective against the MP3 strain following a single dose.^{17,18} However, milbemycin oxime was 100% against MP3 strain when 3 consecutive monthly doses were given.¹⁸ Additionally a bioassay conducted at Auburn has identified microfilariae from dogs that appear to be less susceptible to macrocyclic lactones.¹⁹ A bioassay conducted at the University of Georgia on L₃ from dogs with

suspected preventive failure did not provide evidence of reduced susceptibility.¹⁹ Genetic analysis of microfilariae from dogs that had experienced unexpected preventative failure had significant genetic changes (loss of polymorphism) as compared to microfilariae with known susceptibility.^{20,21}

Every compound currently marketed in every form of administration (oral, topical, and parenteral) has been shown to be less than perfect in at least one study (American Heartworm Society Jan 2014).

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