Dirofilariasis - "Heartworm Disease"

Hosts and Geographic Distribution
- Dogs, coyotes, cats, ferrets, fox, etc.
- Worldwide in tropical, subtropical and temperate zones.
- U.S. reported in all 50 states (endemic at least regionally in all states but Alaska) & Canada
- In a national survey veterinarians in the United States reported over 255,000 dogs diagnosed with heartworm infection in 2004 (12,173 clinics reported out of approx 25,000 clinics).
- Highest incidence S. East and Mississippi Valley.
- Lowest incidence in Rocky Mountains, Pacific North West, upper plains states and central Canadian provinces.
- This disease has spread and continues to spread due to increased transportation of dogs from southern enzootic areas, and decrease in mosquito control programs because of societal concerns about the use of outdoor pesticides.
- 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 and several Canadian Provinces. In one study of over 3,000 dogs and cats, 48.8% of dogs and 4.0% of cats relocated were heartworm positive.
- *D. immitis* is now widespread across California with several recognized mosquito vectors (primarily *Ochlerotatus (Aedes) sierrensis*) and coyote reservoirs.
- [://www.heartwormsociety.org/](://www.heartwormsociety.org/)

Adults occur naturally in pulmonary arteries and occasionally the right heart; occasionally aberrant migrations 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)

Female *D. immitis* in pulmonary arteries and occasionally the right heart deposit microfilariae (L₁) into circulation.
1. Microfilariae (L₁) may survive up 3.5 years in the vascular system.
2. Mosquitoes (> 70 species) I.H. become infected when they feed on an infected dog and consumes blood containing the microfilariae (L₁).
3. Microfilariae (L₁) then develop first in mid-gut & then in malpighian tubules of the
mosquito from the L₁ – L₂ – L₃ infective stage within 13 to 30 days.
4. L₃ infective larvae then migrate to the salivary glands of the mosquito
5. Infected mosquito bites dog and deposits infective L₃ larvae in or around the bite wound.
6. L₃ reside in subcutaneous tissues and molt to the L₄ (1.5mm) in subcutaneous tissues within 3 – 12 days.
7. L₄ reside in subcutaneous tissues or muscle of abdomen or thorax and molt to the adult (juvenile adults 1.2- 1.5cm) within 45 – 70 days.
8. Immature adults (2 – 4cm long) migrate to pulmonary arteries and heart by 70 – 90 days P.I.
   - With low to moderate worm burdens worms naturally located in lobar arteries and main pulmonary artery. With heavier worm burdens (≥10) worms appear in right ventricle.
9. Worms mature (12 – 30cm) and then male and female D. immitis mate and females begin depositing microfilariae (L₁) within 6 months (rarely) but more commonly 7 – 9 months P.I.
   - In dogs adult D. immitis may live 5 – 7 years

   - Transplacental migration of microfilariae has been reported in dogs with microfilariae seen in peripheral circulation of neonatal pups. These microfilariae will not mature unless they are ingested by a mosquito & transferred to a host as L₃.

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). Antigen tests ELISA, immuno chromatographic and hemagglutination test systems are available for detecting circulating heartworm antigen. While specific antigens are company secrets it is reported that all antigen tests detect a protein produced by mature female worms (uterine antigen). Circulating heartworm antigenemia and microfilaremia appear for the first time about 5 and 6 months post-infection. 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. Generally there is no need or justification to test a dog for antigen or microfilariae prior to 7 months of age and retesting following treatment should be delayed up to 6 months.
False positives and false negatives may rarely occur. 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). Infections with 3 - 4 female worms 90 – 94% depending upon the specific test. Other than low worm burden the most common cause of false negatives is laboratory error. False positives can occur in well type tests due to inadequate washing. False negatives can occur due to not allowing tests to warm to room temperature before using. In addition false negatives may occur due to low worm burden or unisex infections. To date no antigen test is capable of detecting male worms (even up to 25 males in one study). Always read test labels and directions carefully.

Tests for microfilariae. Used to recover *D. immitis* microfilariae from blood. Often will not be positive until 6 – 9 months post infection when microfilariae are produced. Low correlation between number of microfilaria and number of adults present. Blood should be drawn in the afternoon due to nocturnal periodicity of microfilariae.

Treatment:
Steps to manage the treatment of dogs infected with heartworms consist of the following:
1. Diagnostic evaluations (before therapy) to determine sub clinical disease, Chest radiographs, serum chemical profile, routine fecal exam etc.
2. Preventive medication & administration of a macrocyclic lactone should begin as soon as the dog is diagnosed with a heartworm infection
3. Adulticidal therapy to eliminate mature worms
4. A forced rest period of 4-6 wk to allow the dog to recover from the lung injury associated with worm death
5. An antigen test 6 months post-treatment to determine success of adulticidal therapy & a test for microfilariae to determine success of microfilaricidal therapy if necessary

Heartworms either die in the right heart, pulmonary arteries and lung. Dead and dying parasites usually cause some degree of pulmonary embolism, immunological reaction in lung tissue and possibly death. Following treatment with an adulticide adult worms begin to die and disintegrate within a few days with post-treatment complications commonly occurring within 10 days.

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*. Immature adults are apparently not susceptible to the effects of the drug.
- **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)
  - Two IM doses over 24 hr. 90.7% effective against total worm burden but may clear only 50% of dogs of infection. Male worms are more susceptible to Melarsomine than females. This dosage regimen is less effective than the 3 dose regimen and has a higher rate of post-treat
thromboembolisms than 3 dose regimen.

- 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.**

Prolonged (16 – 30 months) monthly administration of the macrocyclic lactone (macrolides) preventives Ivermectin (6µg/kg) or Ivermectin & pyrantel pamoate killed 56 – 98% of experimentally transplanted 7-month-old adult *D. immitis* and 71% of *D. immitis* in naturally infected dogs. The adulticide effect of Ivermectin generally requires more than 18 months of continuous administration before 40 - 50% of worms are eliminated. **During this time infection persists and continues to cause disease.** American Heartworm Society – “long term continuous administration of Ivermectin generally is not a substitute for conventional arsenical adulticide treatment.” However, if dog owner declines arsenical therapy and elects to follow such a course of treatment the following should be noted. The results of a recent study indicates that such long-term therapy should not be used in dogs with signs of heartworm disease or very active dogs, and if used in asymptomatic dogs, the dogs should be examined by a veterinarian and radiographic evaluations conducted at least once every four to six months until all of the worms are dead. In addition exercise must be restricted in these dogs. **Not an FDA approved use.**

Wolbachia treatment - in infections with other filarial parasites, treatment with tetracyclines during the first month of infection was lethal to some Wolbachia-harboring filariae, but not to a filariae that did not harbor Wolbachia, and treatment of Wolbachia-harboring filariae suppressed microfilaremia. Similar prophylaxis studies with *D. immitis* have not been published, but in one study, tetracycline treatment of heartworm-infected dogs resulted in infertility in the female worms. Studies to determine the effects of suppressing Wolbachia populations with doxycycline prior to adulticide therapy will be required to determine the clinical utility of this therapeutic approach. **Proposed alternative treatment program with the aim of increasing success of adulticide treatment in heartworm endemic areas.** Hypotheses are 1) 3 months of preventive avermectin therapy prior to adulticide allows immature adults to mature before using Immiticide and 2) Doxycycline therapy to kill Wolbachia that might kill some *D. immitis* or possibly increase efficacy of adulticide and possibly reduce post-treatment complications.
- If the dog is symptomatic, attempt to stabilize the dog.
- Put the dog on heartworm preventative 2-3 months and continue through treatment
- Start the dog on Doxycycline 10 mg/kg q 12h for 4 weeks.
- Start on prednisone prior to Immiticide if symptomatic, or at time of Immiticide if asymptomatic. This is also thought to reduce the lethal complications caused by pulmonary thromboemboli when you hit the dog with Immiticide. The dose of pred suggested is 1mg/kg/day divided bid and tapering weekly.
- After 3 months of ivermectin, one month of doxy, and after starting pred if symptomatic, give one injection of Immiticide. This will kill 30-50% of the worms.
- One month later give 2 injections of Immiticide 24 hours apart. This will kill the remaining worms.
- Enforce strict exercise restriction during the entire period, not just after the Immiticide. Any dog with complications should be caged.

Prevention (Chemoprophylaxis) - Dogs

- The most commonly used heartworm preventives are the macrocyclic lactones (ivermectin, milbemycin oxime, moxidectin and selamectin). These drugs have exceptionally anthelmintic activity against L3 and L4, and as mentioned previously they also have activity against microfilariae and in prolonged use some may kill young adult heartworms.
- 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 lactones anthelmintic. These products may not protect after 45 days of exposure since L4 may initiate molt by 50 days post infection and all have molted by day 70..
- Year-round or seasonal chemoprophylaxis depends on the duration of the transmission season in a given location. Preventive treatment should start at 6-8 weeks of age if seasonal risk warrants it. Continuous, year-round chemoprophylaxis may not be necessary in northern states and Canada where the transmission may be less than 6 months. In areas of North America where the transmission season is more than 6 months, continuous year-round chemoprophylaxis should be considered to enhance compliance and protect dogs.
- 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. While development of resistance is certainly a possibility, too little data currently exists to substantiate resistance causing preventive failure. Lack of historic data to substantiate if these newly identified differences in preventive susceptibility are truly recent developments. Not surprisingly differences in susceptibility (in-vivo & in-vitro) have been identified. Not unlike what has been documented in fleas and ticks. Example: the KS1 flea strain and reduced susceptibility to fipronil, imidacloprid & spinosad.
  - Recent data generated in studies using a D. immitis strain called MP3 (collected in Georgia) have indicated that:
- MP3 strain is more susceptible to Advantage multi® than to other preventives. 100%
at a single dose.
- Ivermectin, Milbemycin & Selamectin preventives were 95% - 99% effective against
the MP3 strain following a single dose.
- Milbemycin oxime was 100% against MP3 strain when 3 consecutive monthly doses
were given.
- Field trials determined milbemycin was 100% effective when use according to label
directions.
- To date Ivermectin, Milbemycin & Selamectin have been shown to be 100% at a
single dose against all other heartworm strains.
- FDA does not allow any company to claim 100% effectiveness with any preventive.
- Data from MP3 indicate that *D. immitis* L₃ & L₄ are not equally susceptible to all
preventives.
- While MP3 is more susceptible to moxidectin, because so few *D. immitis* strains have
ever been evaluated in-vivo for their susceptibility to preventives it is unknown if
differences in susceptibility might be seen in other strains for different macrolides.
- Since data from MP3 indicate that a single dose of preventive may not always be
100%, this supports the need for more prolonged or year-round administration
of preventives in endemic areas.

Note: All macrolide preventives will over time reduce reproductive viability of female
heartworms that might be present and also will within a few hours to a few months kill
circulating microfilariae. Some heartworm positive dogs on a macrolide will become
amicrofilaremic within days. Other dogs may take up to 12 months or longer to become
amicrofilaremic. Once the macrolide is discontinued microfilariae production will resume. Of
all the macrolides Milbemycin oxime at approved preventive dosage will cause rapid die off of
circulating microfilaria and caution should be used when administering to microfilaremic dogs.

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• Trifexis™ (spinosad + milbemycin oxime): FOI


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