

Lectures # 23: *Dirofilaria immitis*: Life cycle, pathogenesis, diagnosis, prevention and treatment.

Objectives:

1. Draw the life cycle of *Dirofilaria immitis* showing the time of development for each stage of the parasite, where each stage of the parasite is located and what drugs are effective against specific stages.
2. Answer questions pertaining to the American Heartworm Society Treatment Guidelines 2014 for dogs and cats.
3. Explain how the antigenemia test works.

Outline:

- I. ***Dirofilaria immitis***: found primarily in dogs, also reported much less frequently in cats, foxes, wolves, coyote, California sea lion and man. Ferrets are easily infected.
 - A. Morphology: Adult worms are long, up to 300 mm, and thin with few distinctive features at the anterior end. Males have a corkscrew shaped tail. Females produce microfilariae, not eggs.
 - B. Life cycle: Adult male and female worms (live up to 8 years) are found in the chambers of the right side of the heart and in pulmonary arteries (massive infections may have adults in the posterior cava). Females produce microfilariae that circulate in the blood for several months. Microfilariae ingested by mosquitoes (many species serve as intermediate hosts) during a blood meal penetrate the Malpighian tubules in the abdomen where they develop to L₃ infective larvae before emerging into the body cavity of the mosquito, this requires about 2 weeks with fastest development at 80°F, continuing develop at slower rate requires sustained average temperature above 65°F. Life span of many mosquito species may be as short as 30 days. If L₁ to L₃ delayed beyond the mosquito life span then **No Transmission**. Infective larvae enter the dermis of a primary host when an infected mosquito takes a blood meal and moult to L₄ in about 3-10 days. L₄ larvae migrate from skin sites to the pulmonary artery over a period of 2-3 months by movement through connective tissue. Moulting to L₅ occurs at 3-4 months and these immature adults enter the pulmonary arteries. Adult females begin producing microfilariae about 6 months after infection.
 - C. Pathogenesis in dogs: The presence of adult worms in the right side of the heart and pulmonary arteries leads to endarteritis and fibrosis of the pulmonary vasculature; i.e., **primarily pathological lesions of the lung**. Physical obstruction of blood flow may lead to exercise intolerance. Thromboemboli due to adult worms or their products also occur in the pulmonary vessels. Large numbers of worms may distend and block the pulmonary artery and may cause congestive heart failure. Worms in the posterior vena cava, “caval syndrom” leads to severe liver and kidney disease, seen as sudden lethargy and hemoglobinuria/hemoglobinemia, fatal in a few days if surgery to remove worms is not performed.
 - D. Diagnosis in dogs: It is not possible at this time to diagnose heartworm infection before patent, or near term patent, infections are present; **no test will be valid or useful in a potential host prior to 6 months of age and 6 months of exposure**. Microfilariae, when present (70 to 80 % of untreated, infected dogs) are detected by modified Knott’s or filter examination of one milliter of whole blood, or one drop of whole blood on a slide with coverslip. Adult worm antigen is detected in serum or whole blood by one of a number of commercial kits having nearly **100% specificity** but **variable sensitivity** for adult female worm numbers less than two. Radiography of the thorax showing heart, vessel and pulmonary changes are important for disease evaluation as well as diagnosis. Echocardiography/Sonography will reveal worms in heart chambers but may not see those in pulmonary arteries because not in field of view. Clinical signs of respiratory insufficiency, weakness, poor condition, cough and exercise intolerance are present in severe infections.

- E. Prophylaxis: Drugs used for prophylaxis by killing L₃ and L₄ before they mature in the dog:
1. Ivermectin with (HeartGard Plus) or without pyrantel (HeartGard) at 6 - 12 ug/kg once a month;
 2. Milbemycin for heartworm, intestinal nematodes + spinosad for external.
Once a month oral (Trifexis);
 3. Selemectin topical application once a month (Revolution);
 4. Moxidectin (1%-cats, 2.5%-dogs) for heartworm prevention, intestinal nematodes + 10% imidacloprid for fleas. Once a month topical (Advantage multi). Moxidectin in slow-release lipid microspheres for injection every 6 months – Proheart.
- F. Treatment in dogs: Adult worms can be killed with the arsenical, melarsomine, given in two intramuscular injections 24 hours apart, or given as a half dose (single injection) followed 4-6 weeks later by the full dose (two injections). Dogs treated to kill adult worms will form thromboemboli of dead worms being carried into the capillaries of the lungs and therefore must be kept from physical exertion. Dogs are confined for 4 weeks following adulticide therapy. There is an adulticidal effect over several months to years by continuous, year-round use of ivermectin prophylaxis.
- “Soft kill” using long-term continuous prophylaxis dose of ivermectin to shorten adult worm life span. This has potential use for debilitated dogs or dogs with subclinical infections; however, risk of further pulmonary disease increases if dog has moderate to strenuous exercise.

READING ASSIGNMENT: American Heartworm Society Guidelines for dogs and for cats. Online at <http://heartwormsociety.org> pull down “veterinary resources” and select “current canine guidelines” and “current feline guidelines”. Read the full guidelines NOT the summary!

- G. *D. immitis* in cats: Surveys of feral cats have found an incidence of 5 to 10 % in areas of high canine infection rates. **Cats do not tolerate therapy that kills adult worms.** Prophylaxis with ivermectin at 24 ug/kg, milbemycin at 2 mg/kg, selemectin at 6 – 12 mg/kg, or moxidectin has been shown effective in cats. Microfilaremia in cats is short-lived and most diagnoses rely on radiographic evidence. Antigenemia levels are very low and hard to detect, but a positive result is conclusive proof of infection. Antibody tests indicate only exposure to infection NOT necessarily current infection, and survey studies indicate frequent false negatives and false positives in the currently available commercial laboratory and in-clinic tests.

Feline Heartworm Disease	Canine Heartworm Disease
3 to 10 infective larvae of 100 injected become adult worms in 75% of cats.	75 infective larvae of 100 injected become adult worms in 100% of dogs. Adult
Adult worms live 3 – 4 years.	worms live 6 – 8 years.
Many L ₅ reach lung arteries then die.	Most L ₅ grow into adult worms in lung arteries.
First stage acute disease 3-4 months p.i.: lung vascular and parenchymal inflammation, signs of asthma.	First changes in response to adult worms: lung arteries with intimal proliferation.
Second stage in response to adult worm death: pulmonary inflammation, thromboembolism, fatal.	Chronic disease: shortening and thickening of pulmonary arteries, increased right heart pressure, hypertrophy and failure.
Signs: none to transient, respiratory distress, emesis, cough.	Signs: most asymptomatic, easily tired, shortness of breath, weight loss, murmur.
Serology: antigenemia is transient, or detectable in ~ 40%. Antibody tests?	Serology: excellent with antigenemia tests.
Treatment: supportive, diminishing prednisone. No adulticides.	Treatment: good results with melarsomine against adults.

H. *Wolbachia*, symbiotic bacterial parasite of filarial nematodes and insects, required for microfilaria production may contribute to disease pathogenesis. Also, may be useful in diagnosis and as a target for therapy. Treatment targeting *Wolbachia* with tetracycline-type antibiotics (doxycycline) may be useful in combination with prophylaxis dosing of ivermectin prior to adulticide therapy with Immiticide to reduce adult female worm mass by killing *Wolbachia* bacteria that help worms produce offspring, or in reducing pathology and duration of “soft kill” with ivermectin (see two articles at website for discussion).

I. *D. immitis* in ferrets: These animals are easily infected with heartworm and show microfilaremia more readily than cats, but antigenemia tests may still be negative. Radiographic changes are less apparent than in cats. Ivermectin at 6 ug/kg has been used successfully in prophylaxis.