Heartworm disease: Has Wolbachia changed how we treat heartworm disease?
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OVERVIEW
• Filarial nematode infection of dogs and cats – *Dirofilaria immitis* – adults (female worms up to 30 cm in length) live in pulmonary arteries causing respiratory, cardiac, and in some cases, renal disease.
• Adults living in pulmonary artery cause lobar arterial enlargement, obstruction, and tortuosity causing pulmonary hypertension and thrombosis.
• Severity of disease – directly related to the number of worms, host response, and duration of infection.
• Female adult worms release L1 microfilaria into circulation where they can live for up to 2 years; L1 infective stage for the vector, mosquitoes, in which they develop to L3; mosquitoes inject L3 back into dog where they mature and migrate to the heart. PPP = 6 to 7 months (dogs) – longer in cats.
• Prevalence – widespread throughout North America (even Alaska) but much more common in southern States - along the Atlantic and Gulf coasts and Ohio and Mississippi River basins.
• 100% in of dogs not on prophylaxis may be infected in highly endemic regions.
• Low prevalence areas (Northern States) - pockets of infection usually where mosquito vector is common.
• Although *D. immitis* can infect man, infected dogs represent no direct zoonotic potential.

SIGNALMENT
• Mainly affects dogs 3 to 8 yrs old; all breeds but medium to large-breed dogs (those that spend a lot of time outdoors) are most susceptible.
• Most infected dogs are asymptomatic (Class I or perhaps display an occasional cough) so most infections are picked up during routine heartworm antigen screening during wellness checks.

CLINICAL SIGNS
• Class I – dogs show no abnormal findings.
• Class II – exercise intolerance; cough; weight loss; pulmonary changes on thoracic radiography; blood worm might show a mildly reduced PCV (20 – 25).
• Class III – exercise intolerance; cachexia; syncope; tachycardia; perhaps ascites due to right sides heart failure; hepatomegaly; pulmonary and cardiac changes on thoracic radiography; hemoptysis may occur (suggests severe pulmonary thromboembolic); blood work shows a PCV < 20.
• Vena cava syndrome (occurs when vena cava is obstructed by adult worms) can result in hemoglobinuria due to acute hemolytic crisis.

HEMATOLOGY/SERUM BIOCHEMISTRY/URINALYSIS
• CBC: anemia (Class II – mild; Class III – severe); eosinophilia and basophilia are a sensitive indicator of heartworm disease when they occur together; leukocytosis and thrombocytopenia are often associated with severe thromboembolism.
• Serum biochemical profile and urinalysis: Hyperglobulinemia is not a consistent finding; proteinuria (immune complex glomerulonephritis) is common in dogs with severe chronic infection; hemoglobinuria can occur during an acute hemolytic crisis (vena cava syndrome).

SPECIFIC HEARTWORM TESTING
• Heartworm antigen tests are highly specific, sensitive tests that identify adult female *D. immitis* antigen in serum; now the standard screening test in dogs.
• Antigen tests should not be used in pups under 7 months (can take 7 months after infection to develop a positive); test 7 months after the end of the previous transmission season.
• Annual testing is probably unnecessary if dog receiving monthly macrolide chemoprophylaxis; a 3 year testing interval is probably adequate.
• In cats, antigen tests are more specific (positive test result is strong evidence of heartworm disease) than antibody tests; low worm burdens (fewer than 5 worms) and single-sex infections often result in false-negative results; because > 40% of cats with adult infection are
antigen-negative, a negative result does not rule out heartworm disease; risk of false-positive results increases with low prevalence (most of USA) so positive results in low prevalence areas should be confirmed by other diagnostic criteria or second test.

- Antibody Tests detect serum antibodies to immature and adult heartworms; the most sensitive tests for feline heartworm disease; a positive result documents exposure but does not always indicate mature or current infection (positive predictive value = 25%); in cats, can detect male-only and immature infections; this test is the most logical screening test for asymptomatic cats.
- Microfilaria identification tests (Modified Knott’s test, filter tests, and direct smear); about 25% of infected dogs will be missed if use only these tests.

IMAGING
- Thoracic radiology should always be performed to determine the Class of infection and the degree of thromboembolism; pre-treatment radiographs allow determination of amount of thromboembolism occurring as a result of therapy.
- Thoracic radiographic signs: Enlargement of the main pulmonary artery, lobar arterial enlargement and tortuosity (absent in Class I, severe in Class III); parenchymal lung infiltrates of variable severity can help predict degree of thromboembolism; allergic reactions to microfilaria represented by diffuse, symmetrical, alveolar, and interstitial infiltrates.
- Echocardiography is usually unremarkable and not a cost-effective test, but may show dilation of the right ventricle with wall hypertrophy, and the presence of heartworms (parallel linear lines) especially in cats (rarely found in dogs) most commonly in the right pulmonary artery (cats) but also in right ventricle and atria; expertise and high index of suspicion increases sensitivity of test.
- None-selective angiography is best in cats if used at all – of little practical clinical application.
- Electrocardiography may show RV hypertrophy and atrial fibrillation in dogs with Class III infection.

THERAPEUTICS
- Need to assess justification of adulticide treatment in certain patients. e.g. in very old dogs, the outcome of treatment may be worse than the benefit of treating.
- Dogs with thromboembolic complications especially during adulticide administration should be hospitalized.
- Activity should be severely restriction for at least 4 weeks (6 better) after adulticide treatment; confine dogs treated for Class III disease to a cage for 4 weeks, and 1 week for dogs suffering from pulmonary thromboembolic events.
- Pulmonary failure should be stabilized with antithrombotic agents (e.g., aspirin or heparin) and anti-inflammatory doses of corticosteroid; monitor using clinical and radiographic parameters.
- For dogs with Class III disease, treat CHF (with cage rest, diuretics) until stable before adulticide.
- Vena cava syndrome: remove adult worms from right heart and PA via jugular vein by use of fluoroscopy and a long, flexible, alligator forceps; requires an experienced operator but this surgery is really the only effective method of treating dogs with very high worm burdens.

TREATMENT REGIMENS
- Melarsomine dihydrochloride (Immiticide®, Merial) is the drug of choice. It is highly efficacious against both male, female worms and L5 (>90%), but is thought not to be effective against heartworms less than 4 months of age; has low toxicity; treatment can still result in pulmonary thromboembolism (usually 7–30 days after therapy); anorexia (13% incidence); injection site reaction (myositis – 32% incidence but mild and only lasts 1–2 days); lethargy or depression (15% incidence); elevations of hepatic enzymes rare; neurologic damage as a result of local nerve root inflammation from the drug reaching nerve roots close to the injection site (essential to make sure the injection is deep within a muscle body).
- Prior to initiating melarsomine treatment, it is often beneficial to give ivermectin (at prophylactic doses of 6 ug/kg orally) for 1 to 6 months (3 months most often recommended) especially when dogs are clinically stable; this should allow older larvae and immature adults time to develop to an age at which they can be killed by melarsomine (over 4 months at least); it will also greatly reduce circulating microfilaria and migrating larvae, stunt immature worms, and reduce female worm mass, which should reduce the risk of thromboembolism at
the time of melarsomine treatment.

- **Class I infection**: Give 2 injections 24 hrs apart are given into the epaxial muscles (1st on one side, 2nd on opposite side, using 22-gauge needles); apply pressure over the injection site during and after needle withdrawal; antigen test may be checked 7 to 8 months later and if positive, repeat treatment.

- **Class II and Class III infections**: Give 1 injection (kills approximately 40% of worms), then 1 month later, give 2 injections 24 hrs apart (as per for Class I infections); this spreads the worm killing effect of the drug over 2 treatments and reduces the severity of thromboembolism; many veterinarians and teaching hospitals use this schedule for treating Class I infections also.

- Dogs that develop thromboembolism usually present with anorexia, low grade fever, cough, occasionally hemoptysis, which usually becomes evident within 7 to 10 days (occasionally as late as four weeks) after completion of adulticide administration – treat with corticosteroids and rest.

- Ivermectin (at 6 ug/kg orally) has been suggested for use as a treatment for adult heartworms: given monthly for a year, it is about 98% and 95% effective against 3 and 4-month old heartworms (larvae), respectively. Against worms that are 5 months old, ivermectin is over 98% effective if given for 30 months. Against 8 month-old worms (full adults), ivermectin is 56% effective if given for 16 months, and 95% effective if given for 30 months; the older the adult heartworms, the more resistant they are to the effects of ivermectin.

- Long-term administration of ivermectin (at 6 ug/kg orally) or any other prophylactic drug, should NOT be a substitute for melarsomine adulticide therapy because such treated infected dogs often develop worsening clinical, radiographic, and echocardiographic changes.

- The other macrocyclic lactones (milbemycin, salemectin, moxidectin) all are very effective (like ivermectin, close to 100%) 2 to 3 months after infection – good “reach-back” activity so provide a good safety net if prophylactic dosing has been missed – but are NOT effective as adulticides.

- In dogs that still have microfilaria after melarsomine treatment (and pretreatment with ivermectin), attempts should be made to treat these about 4 weeks after giving adulticide.

- Regimen: admit dog to the hospital during the morning, check for the presence of microfilaria, then (if present) give milbemycin (Interceptor®, 0.5 mg/kg) or ivermectin (multiple preparation, 50 µg/kg) orally and watch the patient for signs of microfilarial anaphylaxis (shock; vomiting, diarrhea, circulatory collapse) for the day; discharged in the evening on regular monthly preventative.

- If shock occurs, give shock dose of corticosteroids and IV fluids; prognosis excellent; shock is more likely to occur in those dogs with high circulating microfilaria burdens.

- Ivermectin (at 6 ug/kg orally) will also remove microfilaria from circulation of most dogs but will take 8 months; there is a concern that use of these drugs at doses that allow microfilaria to survive for several months will lead to the development of resistance.

- Begin monthly microfilaricide prophylaxis 4 weeks later – re-infection can occur in treated dogs.

- Antigen test 6 months after adulticide treatment; if positive, reassess the patient to determine the degree of improvement as a result of the first treatment (chest radiographs, strength of positive antigen test, age of patient) and only repeat adulticide treatment if necessary.

- Heparin and aspirin use before and during treatment may not provide any advantages (prevent or lessen thromboembolic events).

- Strict cage rest after melarsomine treatment or during pre-treatment ivermectin can not be over-emphasized.

- The Wolbachia story – Adult *D. immitis* are capable of harboring obligate, intracellular, gram-negative bacteria (genus *Wolbachia* (Rickettsiales); these bacteria can be treated with tetracyclines (doxycycline is drug of choice) – by killing the bacteria, could be lethal to the filarial worms (in one study, tetracycline treatment of heartworm-infected dogs resulted in infertility in the female worms); *Wolbachia* in the adult heartworms might contribute to the pulmonary disease (and even the renal disease) seen in heartworm disease; infected dogs do develop immune responses to the bacteria and bacterial antigens have been found in several organs (lung, liver, kidney).
• **Pre-treat with Doxycycline?** As yet, not enough data. However, recent paper:

Di positive dogs with microfilaremia: Tx with ivermectin (6ug/kg weekly) and Doxycycline (10mg/kg/day from weeks 0-6, 10-12, 16-18, 22-26, and 28-34) resulted in faster decrease in microfilaremia, and higher adulticide activity compared with ivermectin or doxy alone.

- Implications for treatment. If use doxycycline pretreatment with Immiticide, could get a more rapid adult kill off and therefore increase side effects.

- Could initiate doxycycline at time of 2nd Immiticide dose when less adults around.

**Prognosis:**
- Class I and II – excellent.
- Class III – guarded with a higher risk of complications.
- Old dogs may not require treatment, since heartworm infection may not be the life-limiting factor.
- Adulticide treatment - delay in pregnant animals; transplacental infection (microfilaria) can occur.

**PROPHYLAXIS**
- In spite of excellent prophylactic drugs on the market, many dogs (nearly a quarter of a million in one survey of over 18,000 vet clinics) still get infected; prophylaxis should be provided for all dogs at risk.
- In new patients starting on prophylaxis for the first time; use the antigen test as a screening test prior to starting preventive treatment (rule out possible adult infection and antigen test has a much higher predictive value than looking for microfilaria); all antigen-positive dogs should be also tested for microfilariaemia as some macrolide endectocides (milbemycin) may induce a shock syndrome within 24 hours of the first dose; (if positive, consider adulticide treatment options but start prophylaxis treatment immediately).
- Start pups on prophylaxis no later than 8 months of age.

**DRUG OPTIONS**
- Ivermectin (Heartgard®, Merial) – highly effective monthly preventive; retroactive efficacy as long as 4 months after infection when monthly administration is continued for 12 months; when combined with pyrantel pamoate (Heartgard® Plus), also controls hookworms and roundworms.
- Milbemycin oxime (Interceptor®, Novartis); highly effective monthly preventive; also controls hookworms, roundworms, and whipworms; the preventive dosage is microfilaricidal – acute reactions may occur when given to microfilaraeic dogs.
- Moxidectin (ProHeart® tablets, Fort Dodge) monthly preventive; can give to microfilaraeic dogs
- Moxidectin (ProHeart®6 injectable, Fort Dodge); prophylactic effective for at least 6 months after injection; currently not available in the USA.
- Selamectin (Revolution, Pfizer); monthly topical preventive; also controls fleas, ear mites, sarcoptic mange, and some tick infestations.
- Macroicide endectocide preventives (milbemycin oxime, ivermectin, selamactin, and moxidectin) – provide retroactive efficacy of 100% for 1 month and close to 100% for 2 months (see above)
- Diethylcarbamazine citrate (Filaribits®, Pfizer; Nemacide®, Boehringer Ingelheim) – daily administration (6.6 mg/kg) is required to ensure prophylaxis; cheaper than macrocides; need to continue dosing 2 months beyond the end of transmission season; if miss a few doses (which voids protection), administer one dose of a macrolide endectocide (ivermectin, milbemycin etc) at prophylaxis doses.
- All of the prophylactic drugs can be administered safely to collies or collie-like breeds at the appropriate preventive dosages.

**REFERENCES**