Canine and Feline Dirofilariasis: Prophylaxis, Treatment, and Complications of Treatment*

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ABSTRACT: Several agents are available for the prevention of heartworm infection. Melarsomine is up to 96% efficacious (after two doses) as a heartworm adulticide in infected dogs. However, treatment of dogs infected with Dirofilaria immitis can be expensive, and adulticide therapy in patients with moderate to severe heartworm disease can be associated with life-threatening complications. Patients with clinical signs associated with pneumonitis benefit from short-term therapy with antiinflammatory doses of corticosteroids before and after adulticide treatment. Strict cage rest for 4 to 6 weeks is mandatory after adulticide administration. Microfilaricide therapy is indicated for microfilaricemic patients. The prognosis is good in patients with mild to moderate infection, fair to guarded in severe cases, and poor to grave (even with treatment) in patients with caval syndrome, severe pulmonary thromboembolism, or congestive heart failure.

PROPHYLAXIS
Chemoprophylaxis is nearly 100% effective in preventing heartworm infection when administered appropriately. Controversy surrounds recommendations for the proper administration of heartworm chemoprophylaxis based on transmission season and owner compliance. The American Heartworm Society recommends that administration of preven-


catives begin 1 month before transmission season and continue for 1 month after the end of transmission season.1 Geographic location determines the transmission season. Some people advocate year-round prevention to ensure adequate protection. Heartworm chemoprophylaxis is recommended for all dogs and cats living in heartworm-endemic regions.

Macro cyclic lactones (ivermectin, milbemycin oxime, moxidectin, selamectin) are the current agents of choice for chemoprophylaxis in dogs and cats. These medications work by arresting the development of and killing larval heartworms within a few weeks or months of infection. For this reason, macro cyclic lactones provide a

*a companion article on life cycle, pathophysiology, and diagnosis starts on page 133.

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lengthy period of efficacy and may provide protection when lapses in preventative administration occur (i.e., the “reach-back” effect). This reach-back effect provides protection in some cases when administration lapses for a few months because the agents are effective at killing larval stages that take 67 to 80 days to complete. All of the chemoprophylaxis medications are microfilaricidal when administered continuously over a period of time. Although some of the macrocyclic lactones may have an adulticidal effect if used continuously for a prolonged period, long-term use of these agents is not recommended as a means of eliminating adult heartworm infections.

Ivermectin

Ivermectin (canine dose: 6 to 12 µg/kg PO monthly; feline dose: 25 µg/kg PO monthly) kills L3 and L4 larvae during the first 2 months after infection. It has a reliable reach-back effect of 2 months, and this protection may extend to lapses of 3 to 4 months if it is administered continuously for 12 months after the lapse. Ivermectin also appears to be effective at killing immature adult heartworms. Ivermectin's microfilaricidal effect may be accelerated by reducing the dosing interval (at the prophylactic dose) to every 2 weeks or by giving a single dose of 50 µg/kg. Some canine breeds (collies, border collies, Shetland sheepdogs, Old English sheepdogs) appear to be sensitive to ivermectin, with administration leading to neurologic signs, but the doses associated with these signs are typically greater than 16 times the prophylactic dose. Administration of this dose most often occurs when the livestock formulation is used. Studies indicate that ivermectin may have partial adulticidal properties when used continuously for 16 months and may be nearly 100% effective when used continuously for 30 months. However, use of any macrocyclic lactone to eliminate adult heartworm infections is not recommended.

Milbemycin

Milbemycin oxime (canine dose: 0.5 to 0.99 mg/kg PO monthly; feline dose: 2 mg/kg PO monthly) kills L3 and L4 heartworm larvae within the first 6 weeks after infection. It therefore has a reach-back effect of 2 months. Reach-back efficacy after a 3-month lapse followed by 12 months of continuous therapy is 97%; after a 4-month lapse, it is 41%. Unlike other macrocyclic lactones, which have a slow microfilaricidal effect at the preventive dose, milbemycin's effect on microfilariae at the preventive dose is rapid. This rapid effect can result in a mass die-off in animals with a high burden of microfilariae, which can provoke an anaphylactic reaction. For this reason, it is important to know the microfilaremic status of the patient and take appropriate precautions (e.g., cage rest plus observation for 12 to 24 hours after administration) when administering milbemycin to dogs. At preventive doses, milbemycin has also shown efficacy against hookworms, roundworms, and whipworms. Milbemycin may also have partial adulticidal properties when administered continuously long term.

Moxidectin

Moxidectin (minimum canine dose: 2.5 mg/kg monthly as part of topical formulation; minimum feline dose: 1.0 mg/kg monthly as part of topical formulation) was previously available as a slow-release product given as a subcutaneous injection once every 6 months. This product was voluntarily withdrawn from the US market. Recently, moxidectin was reintroduced as part of a topical agent that also includes imidacloprid and is approved for treatment of infections with other internal and external parasites as well as *Dirofilaria immitis*.

Selamectin

Selamectin is a semisynthetic macrolide that is applied topically (6 to 12 mg/kg for dogs and cats) once a month. At the preventive dose, it is effective at preventing heartworm infection as well as killing fleas and flea eggs, sarcoptic mange mites, ticks, and ear mites. Selamectin has a reach-back effect of 2 months and is 99% effective when administered continuously for 12 months after a 3-month lapse. Selamectin causes a gradual reduction in circulating microfilariae when administered according to the manufacturer's directions.

The earliest that heartworm antigen is detectable is 5 months after infection.
TESTING

The earliest that heartworm antigen is detectable is about 5 months after infection. Microfilariae are typically not detected until 6 to 7 months after infection. Animals receiving chemoprophylaxis with macrocyclic lactones may not have detectable antigen until 9 months after infection. For these reasons, it is important to know the local transmission season to help not only in choosing the most appropriate time to conduct testing but also in interpreting test results.

Dogs should be tested for heartworm antigen and microfilariae before chemoprophylaxis is instituted and again for heartworm antigen 6 to 7 months after initiation of therapy. A positive test result before the initiation of therapy indicates current heartworm infection, and the detection of microfilariae at this stage may help avoid complications of chemoprophylaxis administration. If the pretherapy antigen test result is negative but the result of the 6-month test is positive, the animal had a prepatent infection when therapy was initiated. If the animal is antigen negative 6 to 7 months after therapy initiation and reliably receives heartworm preventatives, any subsequent positive test result indicates product failure.

When changing the chemoprophylaxis product for a patient, veterinarians should test the patient at three intervals: (1) before administering the new product to determine heartworm status at the time of product change; (2) 4 months after beginning the new agent to ensure that the previous product was effective; and (3) 9 months after the switch to ensure that the new product is working effectively.

TREATMENT AND COMPLICATIONS IN DOGS

Before treatment is considered in a heartworm-positive dog, diagnostic tests, including thoracic radiography, a complete blood count, serum chemistry, urinalysis, and echocardiography (in cases of suspected caval syndrome or clinically significant pulmonary hypertension), should be conducted to determine the severity of disease and the presence of concurrent disease. The results of these tests will determine the most appropriate treatment for the patient. Regardless of the treatment method chosen, some animals have unpredictable reactions that may be life-threatening. Even with prompt treatment, the lung damage caused by heartworm infection can be irreversible.

Chemoprophylaxis should begin when heartworm infection is diagnosed. This is important to prevent further infection, eliminate microfilariae, and destroy immature heartworms, which are not susceptible to adulticidal therapy. Depending on the time of year relative to the transmission season, some veterinarians elect to treat with chemoprophylaxis for several months before administering adulticide therapy to ensure that all heartworms present are susceptible to the adulticidal agent. It is important to determine whether the patient has circulating microfilariae before administering chemoprophylaxis, as this may affect the choice of agent and the precautions taken (e.g., observation for anaphylactic reaction) when administering the first dose.

Medical Therapy

Melarsomine dihydrochloride (Immiticide; Merial) is the only agent approved for use as an adulticide. It is an organoarsenic compound that is relatively safe and effective as an adulticidal agent. It is administered by injection into the lumbar muscles. Injection-site adverse effects are mild and may include swelling and pain. Two protocols are used for melarsomine administration:

Standard protocol: Two doses of melarsomine (2.5 mg/kg IM) are given 24 hours apart, following the manufacturer’s recommendations. Treatment is followed by at least 1 month of strict exercise restriction.

Alternative protocol: This protocol entails three doses of melarsomine given over a 1-month period. After the initial dose is administered, the patient is discharged with instructions for strict exercise restriction. The patient returns in 1 month for two additional injections given 24 hours apart. This method works by killing some of the worms with the first injection and allowing the dog to recover. The remaining worm burden is eliminated by the second administration of melarsomine. This protocol is

Diagnostic tests are discussed in the article beginning on page 133.
recommended for dogs that have clinical signs of heartworm disease, have evidence of significant heartworm disease, or are thought to be at high risk of thromboembolism. The American Heartworm Society recommends that the alternative protocol be used for all patients because it is safer than the standard protocol. The drawback of this protocol is that it requires 2 months of exercise restriction, added expense for the additional medication, and an increased total arsenic dose.

The most common complication associated with heartworm adulticide therapy is pulmonary thromboembolism (PTE), which results from embolization of the dead worms into the pulmonary vasculature. Clinical signs associated with this event include acute dyspnea, tachypnea, hemoptysis, and, rarely, signs of right-sided heart failure. Thoracic radiography may aid in the diagnosis of PTE by revealing an interstitial infiltrate in the affected lung lobe; however, PTE is often not radiographically evident. Treatment for PTE includes strict cage confinement, oxygen therapy, and possibly corticosteroids. Low-dose heparin therapy may diminish the adverse reactions associated with adulticide therapy, but further studies are necessary to determine its effectiveness.

Antithrombotic agents, such as aspirin, may be beneficial to reduce the severity of vascular lesions, thromboxane-induced pulmonary arterial vasoconstriction, and pulmonary hypertension and to minimize postadulticidal PTE. Recent studies have produced controversial results regarding the benefit of aspirin therapy. The American Heartworm Society does not currently recommend antithrombotic therapy for the routine treatment of heartworm disease.

Surgical Therapy

Surgical removal of adult worms may be elected for animals with very high worm burdens and significant risk of severe PTE. In this procedure, the adult worms are extracted from the right side of the heart using alligator forceps or an endoscopic basket retrieval system introduced into the right atrium and right ventricle via the right external jugular vein. The retrieval instrument should be passed repeatedly until no worms are extracted. Fluoroscopy or echocardiography may be used to assist in visualization of device placement. Adulticidal therapy with melarsomine is typically necessary 1 to 2 months after the surgical procedure because not all the worms can be removed surgically.

In dogs with right-sided heart failure secondary to heartworm infection, the clinical signs associated with heart failure should be addressed before adulticidal therapy is completed. Therapy for right-sided congestive heart failure secondary to pulmonary hypertension includes the use of diuretics (furosemide and spironolactone), vasodilators (ACE inhibitors, diltiazem, hydralazine, or sildenafil), and positive inotropic agents (pimobendan) if myocardial failure is present. The response to therapy depends on the severity of the pulmonary hypertension and right ventricular dysfunction.

Caval Syndrome

Caval syndrome is a relatively uncommon (16% to 20% of dogs), severe complication of heartworm disease.

It is usually caused by retrograde migration of adult worms to the right heart and vena cava, which partially obstructs inflow to the right heart. This results in tricuspid insufficiency, characterized by a systolic murmur, jugular pulses, and an increase in central venous pressure. Concurrent pulmonary hypertension further increases the adverse hemodynamic effects of tricuspid regurgitation (reduced left ventricular preload and decreased cardiac output). Dogs with caval syndrome have a poor prognosis.

Clinical signs associated with caval syndrome include abdominal effusion (ascites), exaggerated jugular pulses, anorexia, hemoglobinuria (considered pathognomonic for caval syndrome), and acute respiratory distress. These signs are usually sudden in onset. Physical examination findings may also include poor mucous membrane color, prolonged capillary refill time, weak femoral pulses, hepatosplenomegaly, heart murmur secondary to tricuspid insufficiency, a split S2, and a cardiac gallop. Clinical pathologic abnormalities include anemia due to destruction of red blood cells as they travel through the worms, increased fragility of red blood cells, hemoglo-
binemia, metabolic acidosis, decreased hepatic function, and impaired removal of circulating coagulants, which may lead to the development of disseminated intravascular coagulation (DIC). Thoracic radiographs are consistent with severe heartworm disease. Treatment includes stabilization of the patient and treatment for concurrent disorders (e.g., DIC), followed by surgical removal of the worms as previously prescribed.

**TREATMENT IN CATS**

Adulticidal therapy for cats with heartworm disease is not recommended at this time. The results of early studies suggest that the use of melarsomine is not safe or beneficial in cats. Cats that are heartworm positive or at risk of exposure should be given heartworm chemoprophylaxis because the consequences of feline heartworm disease are potentially deadly and there are no clear therapeutic solutions. The same chemoprophylaxis agents that are approved by the US Food and Drug Administration (ivermectin, milbemycin, moxidectin, and selamectin) for dogs are also approved for cats. These compounds are administered and work the same way as in dogs. Whether cats need to be tested before initiating chemoprophylaxis therapy is under debate. Although testing is not necessary, it can help determine the local prevalence of heartworm infection. Unlike in dogs, it is not necessary to test cats before and after changing chemoprophylaxis agents because evidence of infection obtained using the most sensitive test (echocardiography) will not change the clinical course of action. Corticosteroid therapy may be beneficial in cats with clinical signs of heartworm disease. For cats in acute crisis, therapy including corticosteroids (prednisolone [1 mg/kg]), oxygen, and bronchodilators (aminophylline [6.6 mg/kg PO q12h], theophylline [4 mg/kg PO q12h], or terbutaline [0.1 to 0.2 mg/kg PO q12h]) should be instituted.

**ADDITIONAL CONSIDERATIONS**

**Aberrant Migration**

Rarely, adult heartworms migrate to locations other than the pulmonary vessels. The clinical signs associated with this migration depend on the migratory path. Treatment depends on the clinical signs and may involve no treatment, surgical excision of the parasite, adulticidal therapy, or symptomatic treatment.

**Wolbachia**

*D. immitis* has been shown to harbor an obligate, intracellular, gram-negative bacterium belonging to the genus *Wolbachia*. This parasite lives within the heartworm and is thought to produce pathology through release of endotoxins and a major surface protein that may induce a specific IgG response in hosts infected by *D. immitis*. This inflammatory response may contribute to the pulmonary and renal inflammation seen in heartworm-infected animals. Studies have suggested that treatment with tetracycline may lead to sterilization of the female worms and death of immature heartworm infections. More research is necessary to determine *Wolbachia*’s role in heartworm disease and to determine the appropriate therapeutic approach.

**REFERENCES**


**ARTICLE #2 CE TEST**

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**I. Which of the following is a rapid microfilaricide at the preventive dose?**

- a. ivermectin
- b. milbemycin
- c. selamectin
- d. melarsomine
2. Chemoprophylaxis therapy with a slow-acting microfilaricidal compound should be initiated in microfilaremic dogs
   a. at diagnosis.
   b. at the beginning of adulticidal treatment.
   c. after adulticidal therapy.
   d. when antigen test results are negative after adulticidal treatment.

3. The most common complication of heartworm treatment with melarsomine is
   a. anaphylactic shock.
   b. right-sided heart failure.
   c. left-sided heart failure.
   d. pulmonary thromboembolism.

4. The surgical approach for removal of adult heartworms is through the
   a. right jugular vein.
   b. left jugular vein.
   c. right femoral artery.
   d. left femoral artery.

5. _______ is/are required only in patients with caval syndrome.
   a. Antiinflammatory steroids
   b. Anticoagulant therapy with aspirin
   c. Worm embolectomy
   d. Ivermectin as a microfilaricide

6. The earliest time that antigen can be detected is _______ months after infection in a dog receiving heartworm preventatives.
   a. 3  c. 6
   b. 4  d. 9

7. Which statement regarding heartworm preventatives is true?
   a. A reach-back effect of up to 2 to 3 months can be achieved with continuous 12-month administration.
   b. Macrolides may have efficacy as adulticides when administered continuously for prolonged periods.
   c. No preventatives are approved by the US Food and Drug Administration as adulticides or for the elimination of microfilariae.
   d. all of the above

8. When changing chemoprophylaxis medications in dogs, follow-up testing should be conducted
   a. before administering the new product.
   b. 4 months after beginning the new product.
   c. 9 months after beginning the new product.
   d. all of the above

   a. the standard (two-dose) protocol with melarsomine
   b. the alternative (three-dose) protocol with melarsomine
   c. long-term treatment with macrolides
   d. embolectomy

10. One species of Wolbachia bacteria
    a. is harbored by adult heartworms.
    b. may induce an inflammatory response in hosts infected with *D. immitis*.
    c. may play a future role in the treatment of heartworm infection.
    d. all of the above