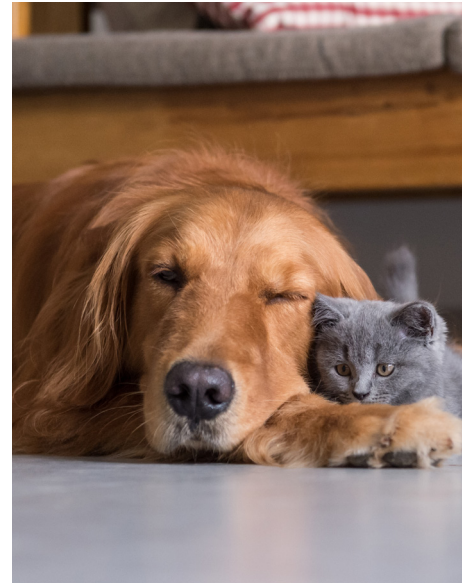


## HEARTWORM: TOP 10 Q&A

The following questions about heartworm infection arise commonly during clinical practice. The answers represent the consensus opinion of the Cardiac Education Group. However, for complete information and recommendations related to this topic, please see the websites of the American Heartworm Society ([heartwormsociety.org](http://heartwormsociety.org)) and the Companion Animal Parasite Council ([capcvet.org](http://capcvet.org)).



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### TOP 10 QUESTIONS:

- 1 Is heartworm infection increasing in prevalence?**
- 2 Is the heartworm parasite becoming resistant to current preventatives?**
- 3 Should I “heat treat” all antigen tests?**
- 4 What role does *Wolbachia* play in heartworm disease?**
- 5 What are the current recommendations for treatment of heartworm infection?**
- 6 Can a combination of doxycycline and a macrocyclic lactone be used to treat adult heartworm infection?**
- 7 How should I care for the patient with clinical signs from heartworm disease, beyond adulticide therapy for the infection?**
- 8 When should I suspect that a dog has heartworm caval syndrome?**
- 9 Is there a national shortage of melarsomine dihydrochloride?**
- 10 What about heartworm disease in cats?**

## 1 Is heartworm infection increasing in prevalence?

Greater prevalence of heartworm infection has been observed throughout the United States over the last decade, expanding the diagnosis to areas of the country not historically associated with the disease. Although the southeast remains the area of the country with the greatest heartworm burden and the disease remains driven by climactic factors and the biology of the mosquito vector, it is important to recognize that changing prevalence factors for this parasite and increased interstate transport and travel of animals from endemic areas have facilitated spread of the disease. It is also worth noting that heartworm infection has been diagnosed in all 50 states.

The prevalence of heartworm positive dogs in the United States was 1.16% in 2012, representing 1 positive result for every 87 tests performed. This increased to 1.28% for 2016, representing 1 positive result for every 79 tests performed. Although a small change, this equates to an increase in positive cases across the country from 69,790 in 2012 to 118,689 in 2016 – a 70% increase in the number of dogs testing positive for this parasite over 4 years. More prevalent testing (9 million tests in 2016 vs. 6 million tests in 2012) accounts for some of this variation in addition to the factors noted above. The above testing data is taken from the Companion Animal Parasite Council ([capcvet.org](http://capcvet.org)).

## 2 Is the heartworm parasite becoming resistant to current preventatives?

In recent years, debate has arisen suggesting a loss of efficacy for the macrocyclic lactones against *D. immitis*, based on reports of dogs that had received preventative developing adult infections. However, a detailed analysis demonstrated that nearly all cases of perceived preventative failure can be explained by a lapse in preventative administration in the preceding months or years.<sup>1</sup> Therefore, most cases of preventative failure are not a failure of the medication, but a failure of compliance.

However, while macrocyclic lactones remain an effective and critical method to prevent heartworm infection, certain strains of *D. immitis* have shown preventive failure for most of the commercially available preventatives in controlled conditions.<sup>2</sup> However, the prevalence of macrocyclic lactone resistance appears to be low, particularly outside of the Mississippi River valley. The current recommendations of the American Heartworm Society support year-round, monthly administration of commercially-available macrocyclic lactones and annual testing to effectively prevent infection and monitor for development of resistance or lapses in compliance. Alternating different preventive formulations has not been shown to prevent resistance and is not recommended.

## 3 Should I “heat treat” all antigen tests?

A study published in 2014 found that a serum sample from a dog with known heartworm infection could be made negative on conventional antigen testing when mixed with serum from a dog with antibodies against *D. immitis*.<sup>3</sup> A study published the same year reassessed 165 banked serum samples of dogs that had tested negative for heartworm antigen; after heat treatment, 7% of these samples became positive for heartworm antigen.<sup>4</sup> This effect has also been shown in cats, with 5 of 6 experimentally-infected cats becoming positive on antigen testing after heat treatment.<sup>5</sup> Heat treatment releases antigen-antibody complexes; such complexes inhibit the ability of the antigen test to detect circulating antigen. Current recommendations suggest heat treatment of any sample in which a negative result does not fit the clinical picture of the patient; it is reasonable to extend this recommendation to include heat treatment of samples from any dog testing positive that has no known history of preventative use and comes from an area known to have high prevalence of heartworm infection. Heat treatment should be performed at a reference laboratory; heat treatment done in-house is an off-label use of the point-of-care test. Annual testing should optimally include both antigen and microfilaria evaluations.

#### 4 What role does *Wolbachia* play in heartworm disease?

*Wolbachia* species are gram-negative bacteria that function as endosymbionts and live within the heartworm parasite, *D. immitis*. This symbiotic organism is required for normal development, reproduction, and survival of all stages of *D. immitis*.<sup>6</sup> Fortunately, these *Wolbachia* organisms are susceptible to doxycycline and this antibiotic reduces *Wolbachia* numbers in all heartworm life stages. *Wolbachia* organisms not only are required for parasite replication, they also contribute to the pathologic response to *D. immitis* in animals. Release of *Wolbachia* during worm death likely contributes to the inflammatory response. Dogs with experimental heartworm infection that have been treated with doxycycline, however, have less severe pulmonary artery pathology after adulticide treatment when compared with dogs treated with adulticide alone.<sup>7</sup>

#### 5 What are the current recommendations for treatment of heartworm infection?

Current guidelines for the prevention and treatment of heartworm infection in dogs and cats are available from The American Heartworm Society ([heartwormsociety.org](http://heartwormsociety.org)).<sup>8</sup> In dogs, the current recommendation begins with confirmatory testing followed by initiation of macrocyclic lactone preventatives and one month of doxycycline (10 mg/kg PO q 12h for 30 days) at the time of diagnosis. Ideally, the dog's microfilaria status is determined, both to determine risk for hypersensitivity reactions and for public health assessment. Approximately 60 days after diagnosis, adulticide therapy is initiated. Delaying adulticide therapy for 60 days allows juvenile worms to reach maturity, at which time they will respond to adulticide, and prevents a "susceptibility gap" caused by an immature infection that is mature enough to survive preventative, but not mature enough to be effected by adulticide. The current approved adulticide therapy is melarsomine dihydrochloride. A 3-dose, staged protocol is recommended for all dogs undergoing adulticide therapy. This approach kills approximately ~99% of adult heartworms, clearing most dogs of adult infection. In comparison, the 2-dose protocol only kills 90% of worms, clearing about 70% of dogs of adult infections and is not recommended. Pre-treatment with doxycycline improves the success rate of both strategies and limits complications during worm death related to *Wolbachia*. Exercise restriction is crucial during treatment as failure to limit exercise in dogs with heartworm infection can lead to exacerbation of pulmonary vascular and parenchymal pathology.

Adulticide therapy with melarsomine should always be recommended in dogs with heartworm infection. However, in animals with severe systemic illness or significant co-morbidities (advanced liver disease, cancer, renal dysfunction, concurrent respiratory illness, etc.) that are expected to limit the dog's lifespan or be exacerbated by adulticide therapy, alternative kill strategies may be considered (refer to question 6). Alternative kill strategies, although not endorsed as a therapy for heartworm infection, may be considered in such cases and consultation with a cardiologist is strongly recommended.

#### 6 Can a combination of doxycycline and a macrocyclic lactone be used to treat adult heartworm infection?

Adulticide therapy with melarsomine is the only recommended adulticide treatment for heartworm infection in dogs. Studies have shown that the macrocyclic lactones have efficacy against adult heartworms when used at preventative doses.<sup>9,10</sup> In Brazil, where melarsomine is not available, adulticide therapy using topical moxidectin/imidacloprid q30 days and 10 mg/kg oral doxycycline q12h for 30 days resulted in some dogs becoming antigen negative within 6 months and all dogs free of heartworm after 24 months of therapy.<sup>11</sup> An abstract reporting treatment of 18 infected dogs in the United States utilized oral doxycycline at 12 mg/kg/day for 15 days with concurrent topical moxidectin/imidacloprid every 15 days for 90 days total, then every 30 days, and found that 13 dogs were antigen negative at a median 208 days of therapy though some remained positive after heat treatment (refer to question 3) for over a year.<sup>12</sup> Similar results have been shown with ivermectin in combination with doxycycline. However, uncertainty regarding the speed of adulticidal effect and ongoing damage to the heart and pulmonary vascular bed, unclear guidelines on exercise restriction requirements, and concern for contributions to macrocyclic lactone resistance are rationale to not pursue such "slow kill" strategies at this time.

## 7 How should I care for the patient with clinical signs from heartworm disease, beyond adulticide therapy for the infection?

Animals with heartworm infection can develop varied clinical signs that require additional therapy that may be short-term but can be life-long in some cases. Right-sided congestive heart failure (CHF) manifests typically as abdominal effusion; mild pleural effusion may also be seen and abdominal or thoracocentesis may be necessary to stabilize the animal. Therapy of CHF secondary to heartworm infection involves furosemide (typically at 2-3 mg/kg PO q12h), an angiotensin-converting enzyme inhibitor (e.g., enalapril or benazepril at 0.5 mg/kg PO q12h), pimobendan (0.25 - 0.3 mg/kg PO q12h), spironolactone (2 mg/kg PO q12h), and in some cases intermittent centesis. As right-sided CHF from heartworm disease is usually secondary to pulmonary hypertension, sildenafil administration may also be beneficial at 1-3 mg/kg PO q8-12h.

Pulmonary hypertension can be a clinical manifestation of heartworm disease, resulting in labored breathing, lethargy, reduced exercise capacity, and syncope. Right-sided CHF may not be present even when pulmonary hypertension is severe. An echocardiogram is recommended to evaluate for the presence and severity of pulmonary hypertension and in some cases to rule-out caval syndrome (refer to question 8). If pulmonary hypertension is documented or suspected based on clinical presentation, sildenafil administration is recommended at 1-3 mg/kg PO q8-12h.

Pneumonitis is a common complication of heartworm infection, resulting in cough and in severe cases hemoptysis or dyspnea. Thoracic radiographs are indicated to evaluate for pneumonitis, which manifests as a patchy to diffuse interstitial pattern throughout the lungs. Treatment is indicated prior to and during adulticide therapy, including a tapering dose of a steroid such as prednisone at 0.5 to 1.0 mg/kg PO q12h for 3-7 days, then 0.5 mg/kg PO q24h for 7 days, then 0.25 mg/kg PO q24h. The higher dose range of steroid should be reserved for dogs with significant respiratory distress or if signs return or worsen during taper. Concurrent doxycycline is advised as would be given for any patient with heartworm infection at 10 mg/kg PO q12h for 30 days.

## 8 When should I suspect that a dog has heartworm caval syndrome?

“Caval syndrome” implies a large worm burden partially obstructing the tricuspid valve orifice, often associated with mechanical intravascular hemolysis. Fortunately, heartworm caval syndrome is relatively uncommon in the dog and quite rare in the cat. Heartworm caval syndrome should be considered a rule-out in dogs with an unknown history or known lapse(s) of heartworm prophylaxis that are with clinical evidence of right-sided CHF with or without significant respiratory distress. The probability increases if they are found to be heartworm antigen positive, have a moderately loud systolic murmur over the right hemithorax, or evidence of hemolysis (port wine color to the urine, hemolysis in a separated blood sample, low PCV). It is important to note that not all patients with caval syndrome will experience all of the listed findings. The presence of any combination of findings warrants the recommendation of an echocardiogram, especially if adulticide therapy is being considered. A basic, focused 2D echocardiogram can easily identify a significant worm burden within the right atrium, ventricle or pulmonary arteries. If worms are identified, the decision to remove them manually is often based on the overall physical mass of worms and the presumption that physical removal would be expected to significantly improve outcome. These patients still require adulticide at a later time, but outcomes are improved if a large number of worms can be removed. Referral of these cases typically constitutes an emergency referral, especially if there is evidence of significant hemolysis. However, stabilization/initiation of supportive therapy (refer to treatment of right-sided CHF above) can be started pending referral. However, initiation of sildenafil should be avoided unless the dog cannot be stabilized without it. Treatment with sildenafil may cause the worms to relocate to the lungs where they cannot be easily removed. Consultation with your local cardiologist in cases suspected to have caval syndrome can be beneficial. Physical removal of the worms is catheter-based and often well tolerated with many dogs experiencing rapid resolution of clinical signs. Long-term outcome is good, provided they survive the procedure and the immediate post-operative period.<sup>13</sup>

## 9 Is there a national shortage of melarsomine dihydrochloride?

In 2011, Merial announced a nationwide shortage of Immiticide® (melarsomine dihydrochloride), the only approved adulticide therapy in the United States, related to technical issues at a production facility. For a time following this announcement, supplies of melarsomine could only be acquired via limited importation of the European-approved product when a proven heartworm positive case was encountered. In February 2017, the FDA approved Diroban™, a generic form of melarsomine distributed by Zoetis, that is bioequivalent to Immiticide®. Both agents can be used as adulticidal therapy for the treatment of heartworm infection in dogs.

## 10 What about heartworm disease in cats?

If heartworm disease is suspected in a cat based on clinical presentation (respiratory distress, cough), an antibody test should be done to confirm exposure. If the antibody test is positive, an antigen test may be useful to document an active infection. Referral to a cardiologist for a focused echocardiogram can be valuable if heartworm disease is suspected. In general, known or suspected heartworm infection in the cat should be treated with anti-inflammatory corticosteroids (2 mg/kg per day for 7 days, then 1 mg/kg per day for 7 days, then 0.5 mg/kg per day for 14 days), doxycycline at 5 mg/kg PO q12h, and heartworm prevention initiated with an approved macrocyclic lactone. Melarsomine therapy is contraindicated in the cat. In cats that continue to have clinical signs or develop severe clinical signs during treatment, consultation with a cardiologist is strongly recommended to assist with definitive diagnosis and therapy.

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