Banfield PET HOSPITAL

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Banfield Applied Research & Knowledge Team

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Literature Review – Heartworm Disease

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INTRODUCTION AND LIFE CYCLE

Canine and feline heartworm disease is caused by the filarioid nematode *Dirofilaria immitis*.[1] The parasite can be found in warm climates worldwide and is widespread throughout the United States.[2-4] Indeed, data from Banfield's PetWare database show positive heartworm antigen test results in every state in which a Banfield hospital is located.

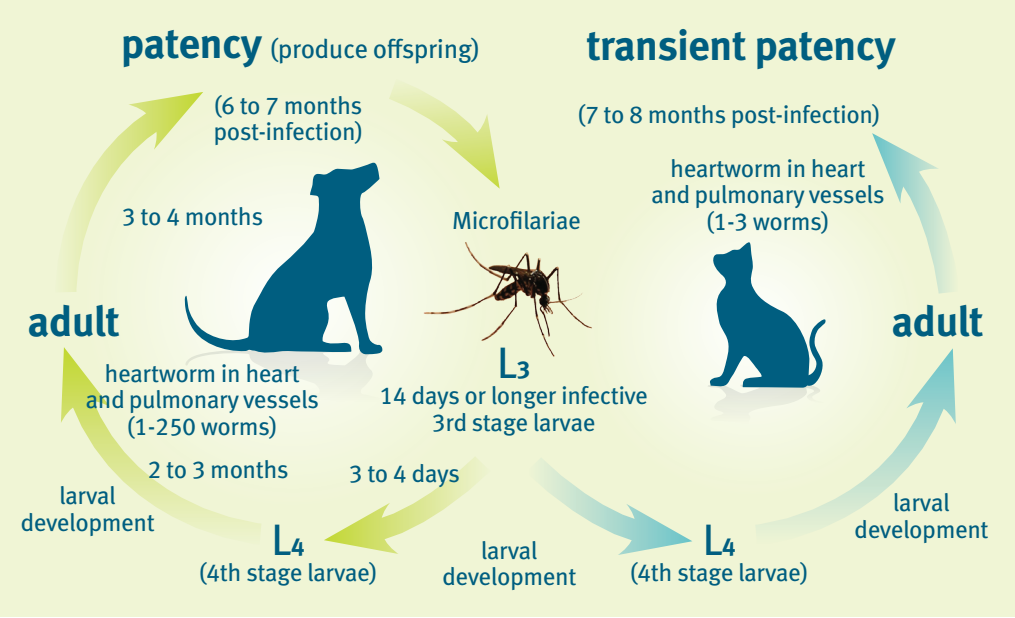
The life cycle of *D. immitis* (*Figure 1,* page 2) begins when a female mosquito bites an infected host, ingesting microfilariae (L1 larvae) circulating in the bloodstream.[1] Microfilariae develop within the mosquito, with the rate of development dependent on the ambient temperature. At 79^{0}F (26^{0}C), the molt to the L2 stage occurs about 10 days after ingestion, and the molt to L3 occurs about 13 days after ingestion.[5] Larval development ceases below 57^{0}F (14^{0}C).[5] Approximately 17 days post-ingestion, the L3 larvae migrate to the mosquito's head and mouthparts. *D. immitis* is then transmitted from one animal to another when the infected mosquito feeds on the new host. Infective L3 larvae rupture from the mouthparts and are deposited on the skin of the host surrounded by a droplet of hemolymph. The larvae then penetrate through the wound left when the mosquito withdraws her mouthparts.[1]

The L3 larvae continue their development in the subcutaneous tissues of the host, migrating to the abdomen and thorax as they molt to L4 and L5 stages. The molt to L4 occurs anywhere from three to 12 days after infection, with the molt

CLINICAL BOTTOM LINE

- Heartworm disease is caused by *Dirofilaria immitis* and affects dogs and cats, as well as a variety of animals in the wild. *D. immitis* is transmitted from one animal to another by mosquitoes.
- *D. immitis* is endemic in at least localized areas of all 48 contiguous states of the United States. In some states, the parasite is endemic throughout most of the state.
- Clinical signs in dogs are similar to those of right-sided congestive heart failure, *e.g.*, cough, lethargy, difficulty breathing and sometimes hemoptysis. Many cats have no clinical signs, however infected cats may exhibit signs of acute respiratory distress or may die suddenly. Indoor housing does not protect cats from infection.
- Diagnosis of canine heartworm disease is usually by antigen test, which detects proteins from the reproductive tract of adult female worms, and is often supported by diagnostic imaging. Diagnosis of feline heartworm disease can be challenging and relies on a combination of multiple tests.
- Treatment of heartworm disease is not simple and can result in serious complications. Adulticide therapy with melarsomine is usually the treatment of choice in infected dogs. In cats, there is no safe adulticide; the aim of therapy is usually to reduce the severity of clinical signs while the patient recovers.
- The American Heartworm Society (AHS) recommends year-round chemoprophylaxis in the form of either monthly medication (topical or pill) or twice-annual injections for all dogs nationwide. Cats in heartworm-endemic areas should receive either form of monthly medication. The AHS also recommends annual heartworm tests for all dogs.
- Compliance is the biggest barrier to the efficacy of preventives but can be improved by tailoring discussions and prevention strategies to the needs of the individual patient and client.

Figure 1: Heartworm Life Cycle



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to L5 occurring 50 to 70 days post-infection. The L5 larvae then penetrate veins and are carried to the heart, arriving 70 to 90 days post-infection. After reaching the heart, the worms continue to grow, with females growing to as much as 10 times their immature length.[6] Worms become sexually mature at about 120 days post-infection, before mating and producing more microfilariae. Microfilariae are detectable between seven and nine months post-infection.[1,6]

Dogs are considered the most competent hosts of heartworm, whereas cats are much less suitable hosts.[6] In cats with patent heartworm infections, microfilariae are also detectable seven to nine months post-infection. However, microfilaremia occurs in only 20 percent of cats with mature heartworms.[7] Adult worms survive for only two to four years in cats, compared with five to seven years in dogs.[8] Cats have smaller worm burdens than dogs, typically harboring six worms or less.[7] In contrast, a study of heartworm-infected dogs in Florida, an area endemic for heartworm disease, showed that more than 52 percent of infected adult dogs had worm burdens of more than 11 worms per dog.[9] Experimentally infected cats also have lower infection rates, smaller worm burdens and reduced survival of microfilariae and adult worms compared with experimentally infected dogs.[7]

PATHOPHYSIOLOGY

The presence of adult worms in the heart leads to thickening of vessel walls and subsequent pulmonary hypertension. Histopathological changes in the vessels of cats infected with heartworm include fibrosis, hypertrophy and thrombosis.[10] In both dogs and cats, sustained hypertension can eventually lead to right-sided heart failure. Pulmonary parenchymal damage also occurs as a result of thrombosis caused by the embolization of dead worms, larvae or microfilariae.[11] This can lead to severe lung damage in cats.[12] Not all worms successfully migrate to the heart; worms are occasionally reported in atypical locations such as the abdominal cavity, eye, spinal cord and brain.[13] Aberrant migration occurs more frequently in cats than dogs. [7]

Clinical disease in dogs is usually slowly progressive, with a gradual onset of signs consistent with right-sided congestive heart failure such as lethargy, cough and abdominal distension due to ascites.[14] Dogs may also suffer from caval syndrome, whereby adult worms migrate from the pulmonary arteries to the right atrium leading to acute right-sided heart failure and death, if untreated.[15] Signs of caval syndrome include collapse, anemia, hemaglobinuria, jugular pulsation and characteristic heart murmur. Signs of disease due to heartworm infection in cats are much more variable. Many cats do not show clinical signs, although infected cats may develop respiratory disease, neurological signs or vomiting, or may die suddenly.[8,16] Cats may show signs even when infected by immature

worms or a single adult worm.[17] Right-sided congestive heart failure and caval syndrome have also been described in cats, but occur only rarely.[18,19]

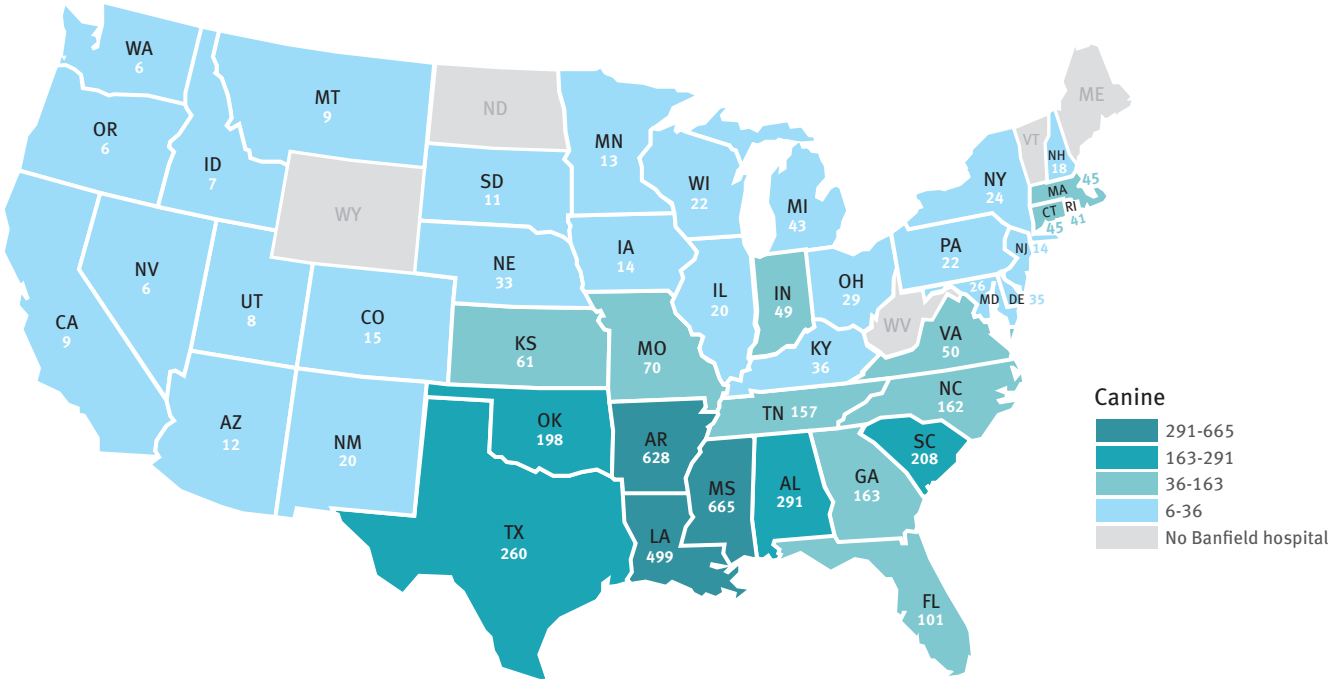
Cats may experience acute episodes of coughing, dyspnea or intermittent vomiting, known as feline heartworm-associated respiratory disease (HARD), at around three months post-infection.[20] Since most immature worms do not survive in cats after they reach the caudal pulmonary arteries, it is thought that this acute disease is related to the death and embolization of worms or worm fragments.[20] This induces a strong inflammatory response in the vessels and pulmonary parenchyma with subsequent infarction of the pulmonary parenchyma and circulatory collapse.[20,21] Other signs of HARD may include neurological signs (*e.g.*, ataxia, head tilt, blindness, circling or seizures) and sudden death.[20] Cats infected with heartworm often self-cure; in a study of 34 naturally infected cats with subclinical disease, 28 (82 percent) self-cured, and 21 of these showed no clinical signs during the study.[20] However, it should be noted that four of the six cats that died during the study showed no overt clinical signs before death.[20]

Dogs and cats are not the only species susceptible to heartworm infection. Natural infections have been reported in wild felids, including the African leopard, tiger, bobcat, snow leopard and African lion; ferrets and wild mustelids; monkeys; and marine mammals and rodents. Dogs, however, are the most frequently infected and have the highest worm burdens.[6,22,23] Ferrets are also highly susceptible to infection and even a few adult worms can cause severe disease or death.[23] Zoonotic infections have been reported worldwide and usually occur in heartworm-endemic areas.[1,6] Humans are aberrant hosts for *D. immitis* and migrating larvae typically cause subcutaneous, ocular or pulmonary disease syndromes.[1] Pulmonary migration of worms usually causes respiratory signs and the subsequent pulmonary granuloma can be seen on chest radiographs as a "coin" lesion.[6] Worms may occasionally migrate to other locations, with uncomfortable consequences.[24]

The immunopathology of heartworm infections is not well-understood. *In vitro* studies on peripheral blood lymphocytes in dogs and pulmonary intravascular macrophages in cats suggest that heartworms and microfilariae induce immunosuppression.[25,26] However, it has been observed that worm burdens in dogs living in endemic areas seem to reach a natural limit and that worms survive longer in naturally infected cats than in cats experimentally infected with greater worm burdens than would occur naturally.[1,7,8] These observations, coupled with the fact that many cats self-cure, would suggest that the immune system is capable of mounting a response to heartworms or microfilariae to at least moderate the severity of infection.

Much of the recent focus on heartworm immunology and pathophysiology has been on the role of *Wolbachia*. *Wolbachia* is an intracellular gram-negative bacterium belonging to the order Rickettsiales and is an endosymbiont of some pathogenic filarioid nematodes.[27,28] Antibodies against *Wolbachia* surface protein (WSP) have been detected in naturally infected dogs and cats.[29,30] In experimentally infected cats, anti-WSP antibodies remain high after antibodies to *D. immitis* have waned.[30] *Wolbachia* certainly plays a role in the pathogenesis of canine and feline heartworm infection, although the precise role is unclear. Treatment of experimentally infected cats with ivermectin increases anti-WSP titers even further,[30] suggesting that death of the worms releases *Wolbachia* organisms and stimulates a strong host immune response.[30] Treatment with doxycycline and ivermectin prior to melarsomine administration reduces the severity of lung pathology in heartworm-infected dogs.[27,31] In a study of naturally infected cats and dogs, there was no clear difference in lung pathology between animals with circulating anti-WSP antibodies or detectable WSP antigens in their lungs and those that did not have detectable levels of WSP antigen or anti-WSP antibody.[27] However, arterial lesions were found to be less severe and thrombi much less numerous in experimentally infected dogs treated with a combination of doxycycline and ivermectin

Figure 2: Prevalence of Positive Heartworm Tests by State—Banfield Data (cases per 10,000)



prior to melarsomine administration than in dogs left untreated or those treated with melarsomine alone.[27] These findings suggest that rather than contributing to pathology while worms are alive, *Wolbachia*'s contribution to the pathological effects of heartworm infection may be related to the host's immune response when worms die and release the bacteria.

EPIDEMIOLOGY

D. immitis can be found in warm climates worldwide.[6,13] In the United States, the prevalence of canine and feline heartworm varies from state to state but positive antigen test results have been recorded in dogs in all 50 states, and *D. immitis* is considered to be endemic in at least localized areas in each of the contiguous 48 states.[3,4,32]

In a survey using an antigen test, the reported prevalence of heartworm infection in owned dogs varied between 0.1 percent in South Dakota and 7.4 percent in Mississippi.[4] Results of antigen and microfilaria concentration tests performed at Banfield hospitals in 2010 show a prevalence of between 0.06 percent in Nevada, Oregon and Washington and 6.65 percent in Mississippi (*Figure 2*). Prevalence estimates can vary greatly depending on the area chosen, sampling method and population. For example, Bowman, et al. (2009) reported a prevalence of 0.6 percent in owned dogs in Indiana that underwent an antigen test, whereas Levy, et al. (2011) found that 48.8 percent of antigen test results in stray dogs relocated after Hurricane Katrina were positive.[4,33]

The prevalence of feline heartworm is considered to be 9-18 percent of the prevalence of canine heartworm in a given area.[34] However, feline heartworm prevalence is much more difficult to estimate accurately, given that infected cats often have no signs or self-cure and that infected cats may die suddenly without signs of heartworm infection.[8] From samples submitted to a commercial diagnostic testing service, the prevalence of feline heartworm infection in the United States has been estimated between 0.5-1.4 percent using antigen tests and between 1.1-8 percent using antibody tests.[35] Necropsy surveys of shelter cats in endemic areas of northern Georgia and Florida revealed adult heartworms in 2.1-4.9 percent of necropsied cats, respectively.[36,37]

Published risk factors for canine heartworm infection include dog origin (owned vs. stray or shelter), increasing age, breed type (sporting breeds) and outdoor exposure.[1,38] Miller and Crosbie (2011) found that dogs that spent more than 50 percent of the time outdoors during the day were significantly more likely to be diagnosed with heartworm infection.[38] Prevalence has been reported to be much greater in dogs and cats from shelters than in owned pets, sometimes as high as 50 percent.[33,36,39] Gender does not appear to be a risk factor in either dogs or cats.[16,38] It should also be noted that although outdoor activity increases the exposure to vectors of *D. immitis*, indoor housing does not protect against infection; Atkins, et al. (2000) found that 13 of 48 (27 percent) of infected cats were housed exclusively indoors.[16]

Although *D. immitis* has been detected in each of the contiguous 48 United States, infection prevalence, vector distribution, rate of worm development and size of worm burdens vary depending on geography and climate.[4,40-42] As an example, the mean worm burden of heartworm-infected dogs examined at necropsy in Michigan was reported to be 14 worms as compared with a mean burden of 23 worms in Florida.[9,40] The majority of the infected dogs in Michigan (60 percent) had worm burdens of ≤10 worms, whereas 52 percent of infected dogs in Florida had 11 worms or more.[9,40] Mosquitoes' optimal temperature range is 77^{0}F-81^{0}F (25^{0}C-27^{0}C) and rainfall and humidity determine the prevalence of mosquitoes and the number of heartworm larvae they carry.[42-44] Research into larval development in a range of mosquito hosts suggests that infected mosquitoes are unlikely to survive more than 30 days in the wild and that the lowest temperature threshold for larval development is 57^{0}F (14^{0}C).[5] Models that have been developed to predict the seasonality and geography of heartworm infections use units called heartworm development units (HDUs). One HDU is a day when the mean daily temperature is 34^{0}F (1^{0}C) above the threshold of 57^{0}F (14^{0}C). Predictive models are generally based on the assumptions that development ceases below 57^{0}F (14^{0}C), that infected mosquitoes survive for a maximum of 30 days in the wild and that 130 HDUs are required within a 30-day period for the development of infectious larvae.[42] Based on these assumptions, the seasonality and geographic extent of heartworm infections have been predicted in Europe, the United Kingdom, Italy, Argentina and in the state of California, according to published literature.[41,42,45-47]

DIAGNOSIS

Diagnostic tests available for the detection of canine and feline heartworm disease include antigen, antibody and concentration tests, as well as radiography and echocardiography.[32] Antigen tests detect proteins from the reproductive tract of adult female worms and have high sensitivity and specificity in dogs.[32] However, the reported sensitivity of antigen tests varies according to the prevalence of *D. immitis*. In two studies of naturally infected dogs with low worm burdens (one to four and one to 10 adult worms, respectively), the reported sensitivity of antigen tests varied between 78-84 percent and 52-67 percent.[48,49] The reported specificity was 97 percent in all tests used in the first study and between 96-98 percent in the second.[48,49] The reported sensitivity of antigen tests in naturally infected cats varies between 79-86 percent, with reported specificity between 98-99 percent.[50]

Antibody tests detect antibodies produced as part of the host's immune response to the parasite. Antibody tests are typically used in cats, with a reported sensitivity between 62-72 percent and specificity between 81-98 percent.[50] Concentration and filtration tests, such as the modified Knott test, detect microfilariae by passing a sample of blood through a filter in order to capture and concentrate circulating microfilariae.[32] They are considered much less sensitive than antigen tests, though, as 10-67 percent of dogs with adult worms do not have circulating microfilariae and the period during which cats are microfilaremic is very short.[51] False positive concentration tests can occur when dogs are infected by non-pathogenic filarial species

such as *Acanthocheilonema reconditum* (formerly *Dipetalonema reconditum)* and the microfilariae are incorrectly identified.[32]

Radiography and echocardiography are useful adjunctive tests that can provide further evidence of heartworm disease when clinical suspicion is high but diagnostic tests are inconclusive.[52] Radiographic abnormalities seen in cases of canine heartworm disease include enlargement of the right ventricle, main pulmonary artery and parenchymal pulmonary arteries.[53,54] The parenchymal pulmonary arteries may also become tortuous and truncated. There may be a nodular or unstructured interstitial pattern in the lung fields, and hepatomegaly and ascites may be seen if right-sided heart failure is present.[53,54] Radiographic changes seen in cats with heartworm disease are similar, although they occur less consistently, and an absence of radiographic abnormalities does not rule out heartworm disease in cats.[55] Echocardiography of heartworm-infected patients demonstrates hyperechoic parallel lines caused by reflection of the ultrasound waves by the worms' cuticle.[56] These can be visualized in the pulmonary arteries or chambers of the heart.[52,56] The sensitivity of echocardiography for antemortem diagnosis of heartworm infections is highly operator-dependent and is also affected by the number of worms, but has been reported to be as high as 95 percent.[52,56] False positive results can occur with echocardiography and are thought to be caused by the right ventricular chordae tendinae.[56] Alternatively, it is possible that these false-positives were caused by small worm burdens that were eliminated prior to necropsy.[56]

No matter which diagnostic tests are selected, results must always be interpreted in light of the biology of the parasite, prevalence of infection in the local area and other factors that affect test performance. There are four types of occult infections: prepatent infection, naturally occurring unisexual infection, drug-induced unisexual infection and immune-mediated clearance of microfilariae.[57] Antigen and microfilarial tests will return a false negative result if the infection is prepatent (adult female worms are not yet sexually mature and producing microfilariae) or unisexual with only male worms present. Antibody tests are more useful in prepatent infections but will return a false positive result if worms have died but antibody levels have not yet declined below the limit of detection.[58] Antibody tests will also return a false negative result if the patient is infected but has not yet developed sufficient levels of antibody.[50] Combining antigen and antibody tests increases both sensitivity and specificity.[17] Other factors affecting test performance include operator skill, test performance over time and sample handling and quality.[59]

The positive predictive value of a test, the chance that a patient with a positive test result actually has the disease, varies according to disease prevalence.[60] For example, based on published values for sensitivity and specificity of 84 percent and 97 percent, respectively, the positive predictive value of a heartworm test in Louisiana [prevalence of 499 positive tests per 10,000 tests (Banfield data)] is 60 percent.[49] In contrast, the positive predictive value of a heartworm test in Washington [prevalence of six positive tests per 10,000 tests (Banfield data)] is only 2 percent. This means that even in a state with a high prevalence of heartworm disease, there is a 60 percent chance that a dog with a positive heartworm test result is actually infected. Conversely, there is a 40 percent chance that this result is a false positive. It should be noted that the negative predictive value—the chance that a patient with a negative test result is actually disease-free—is very high in both Louisiana and Washington: 99.1 and 99.9 percent, respectively. This means that a negative test result generally provides good evidence that the patient is disease-free. However, positive test results should be confirmed with additional diagnostic tests such as repeat antigen tests or radiography.

Diagnosis of feline heartworm disease can be likened to piecing together a jigsaw puzzle. Often, a number of tests are necessary, and their results are rarely

considered definitive; they simply raise or lower the index of clinical suspicion. The interpretation of the various diagnostic tests in feline heartworm disease is presented in *Table 1* below, and *Figure 3,* page 8.

TREATMENT

Because of the differing nature of clinical disease in dogs and cats, the recommended treatment differs between the two species. The primary goals of treatment in both dogs and cats are to improve the patient's clinical condition, eliminate heartworms of all life stages and minimize post-treatment complications.[32]

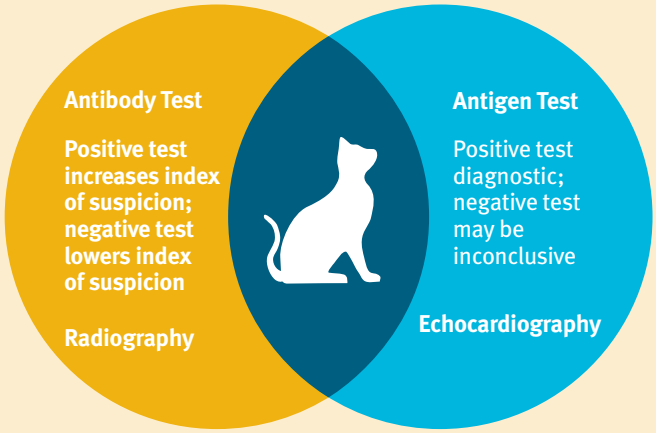
Adulticidal therapy with melarsomine dihydrochloride is standard for dogs, and melarsomine is the only drug approved by the U.S. Food and Drug Administration (FDA) for killing adult heartworms.[32] However, melarsomine is reportedly very toxic to cats and thus is currently not recommended for use in cats.[61] Treatment of cats with ivermectin is possible, but adulticidal therapy in cats is still considered to be a last resort.[62] Medical treatment in both dogs and cats begins with thorough patient assessment and stabilization if necessary. A detailed history and physical examination are mandatory, and standard laboratory tests may help to clarify the patient's clinical state and shed light on the presence and effect of concurrent diseases.[32] Diagnostic tests may be performed prior to and during therapy and will usually include at least antigen testing and thoracic radiography.[32,62] Stabilization may include corticosteroids, intravenous fluids, bronchodilators and supplemental oxygen.[32,62]

Most complications associated with therapy in both dogs and cats are thought to be associated with the embolization of worm fragments and the resultant immune reaction.[20] In canine adulticidal therapy, the

Table 1: Interpretation of Heartworm Diagnostic Procedures in the Cat

Test	Brief Description	Result	Interpretation	Limitations
Antibody test	Detects antibodies produced by the cat in response to presence of heartworm larvae. May detect infections as early as 8 weeks post-transmission by mosquito.	Negative	Lowers index of suspicion	Antibodies confirm infection with heartworm larvae, but do not confirm disease causality.
		Positive	Increases index of suspicion; 50 percent or more of cats will have pulmonary arterial disease; confirms cat is at risk.	
Antigen test	Detects antigen produced by the adult female heartworm.	Negative	Lowers index of suspicion.	Immature or male-only worm infections are rarely detected.
		Positive	Increases index of suspicion.	
Thoracic radiography	Detects vascular enlargement (inflammation caused by young L5 and, later, hypertrophy), pulmonary parenchymal inflammation and edema.	Normal	Lowers index of suspicion.	Radiographic signs subjective and affected by clinical interpretation.
		Signs consistent with feline heartworm disease	Enlarged arteries greatly increases index of suspicion.	
Echocardiography	Detects echogenic walls of the immature or mature heartworm residing in the lumen of the pulmonary arterial tree, if within the visual window of the ultrasound.	No worms seen	No change to index of suspicion.	Ultrasonographer experience with heartworm detection appears to influence accuracy rate.
		Worms seen	Confirms presence of heartworms in the structure.	

Figure 3: Diagnostic Test Interpretation in Cats



Note: In the cat, no single test will detect all heartworm cases. While the antigen tests are highly specific for detecting adult heartworm antigen, they will not detect infections with only live male worms. The clinician must use a combination of test results to determine the likelihood of heartworm disease as the etiology of the cat's symptoms.

Adapted with permission from the American Heartworm Society, www.heartwormsociety.org.

likelihood of thromboembolic complications and the outcome of treatment are related to the severity of infection, the extent of pulmonary vascular disease and the activity level of the dog.[32] Complications are most likely to occur in heavily infected dogs displaying clinical signs, with radiographic evidence of pulmonary arterial obstruction.[32] The American Heartworm Society (AHS) recommends the use of a disease staging system (*Table 2*) to quantify the risk associated with adulticidal therapy in dogs, along with a three-injection alternative protocol and exercise restriction for an extended period of time after treatment.[32] Use of a staging system allows clinicians and clients to better understand the severity of clinical disease, manage expectations of treatment success and reinforce the importance of exercise restriction. The three-injection alternative protocol allows the maturation of larvae that would otherwise not be susceptible to melarsomine and reduces the impact of worm emboli on the lungs by breaking up the treatment into two stages.[32] Using this protocol, one injection of melarsomine at a dose rate of 2.5 mg/kg is administered via deep intramuscular injection into the epaxial lumbar muscles. This is followed one month later by two injections 24 hours apart at the same dose and via the same route.[32]

Regardless of the stage of disease or therapeutic plan, exercise restriction should commence as soon as heartworm disease is diagnosed or suspected and should continue until recovery is confirmed.[32] Absolute confinement to a cage or pen is necessary during the first four weeks after administration of melarsomine in order to minimize the risk of complications due to pulmonary thromboembolism.[32] Dogs diagnosed with heartworm disease can also be started on macrocyclic lactone preventives immediately and if the patient's clinical condition allows, adulticide treatment delayed for two to three months.[32] The reasoning is that some larvae are too old to be susceptible to macrocyclic lactones but too young to be susceptible to melarsomine. Immediate administration of macrocyclic lactones will kill circulating microfilariae and the delay in treatment will allow larvae to develop to adults,

Table 2: Stages of Canine Heartworm Disease

Summary of Clinical Signs of Canine Heartworm Disease		
Early infection	Class 1	No signs
Mild disease	Class 1	Cough
Moderate disease	Class 2	Cough, exercise intolerance, abnormal lung sounds
Severe disease	Class 3	Cough, exercise intolerance, dyspnea, abnormal heart and lung sounds, enlarged liver (hepatomegaly), syncope (temporary loss of consciousness from reduced blood flow to the brain), ascites (fluid accumulation in the abdominal cavity), death
Caval syndrome	Class 4	Sudden onset of severe lethargy and weakness accompanied by hemoglobinemia and hemoglobinuria

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at which time they can be killed with melarsomine.[32] There is a theoretical risk of selecting for resistance and additional damage to the lungs during this period. Another approach is to treat with adulticides as soon as the patient is negative for microfilariae. This could be at initial diagnosis or after treatment of microfilaremia. Macrocyclic lactones should be used with caution in dogs that have large numbers of circulating microfilariae; pretreatment with glucocorticoids and antihistamines may help to minimize hypersensitivity reactions.[32]

There is some evidence that treatment of *Wolbachia* organisms with doxycycline can improve clinical outcomes in dogs. Kramer, et al. (2008) demonstrated that dogs treated with doxycycline and ivermectin prior to melarsomine therapy had less severe pulmonary pathology than dogs treated with doxycycline alone or melarsomine alone.[27] Bazzocchi, et al. (2008) also reported that this same protocol was adulticidal, with a 78 percent reduction in the number of adult worms over a 36-week period.[31] The AHS currently recommends that if doxycycline is used as part of a heartworm treatment protocol, it should be given prior to melarsomine administration so that the organisms and their metabolites are reduced when worms die and fragment.[32] A combination of ivermectin and doxycycline may be used instead of adulticide therapy if melarsomine administration is contraindicated or the patient's condition makes melarsomine treatment difficult. In this case, the AHS recommends that an ivermectin-based preventive be administered monthly and doxycycline be administered daily at 10 mg/kg for four weeks every three to four months.[32] There is also a risk of resistance and additional cardiovascular and pulmonary pathology with this protocol.

Long-term administration of macrocyclic lactones is another potential alternative to melarsomine therapy.[63-65] Studies have demonstrated that monthly administration of a combination of ivermectin with or without pyrantel can reduce worm burdens in naturally infected dogs by up to 71 percent if compliance is maintained for two years.[64-66] Venco, et al. (2004) found evidence of an increase in cardiovascular and pulmonary pathology in heartworm-infected dogs treated with ivermectin and recommended that this treatment be avoided in active dogs or dogs with clinical signs of heartworm disease.[65] Hence, the AHS recommends that if treatment with macrocyclic lactones is chosen over melarsomine, that exercise be restricted and that the dog is examined every four to six months by a veterinarian until confirmed to be free of heartworms.[32] If treatment is stopped prior to elimination of all worms, microfilaremia may reappear.[67] Therefore, strict compliance must be maintained in order to avoid the development of resistance.

Medical treatment of feline heartworm disease is typically based on clinical signs, as adulticidal therapy is associated with a high rate of complications and cats frequently self-cure.[8] In cats with test results consistent with heartworm disease but without clinical signs, prednisone can be administered at 2 mg/kg, tapering down over a four-week period.[62] This approach can be utilized even if there is radiographic evidence of pulmonary pathology, provided cats do not show signs of disease.

Cats with clinical signs of heartworm disease should be stabilized before continuing with therapy. This may include intravenous fluids, intravenous corticosteroids, bronchodilators and supplemental oxygen.[62] Diuretics should be avoided, even if radiographs show severe interstitial or patchy alveolar lung patterns.[62] Once stabilized, treatment can continue as described above based on clinical signs; courses of prednisone may be repeated if clinical signs persist.[62] Despite evidence in dogs that doxycycline may help to reduce pulmonary pathology prior to adulticidal therapy and may be adulticidal in combination with ivermectin, the implications of doxycycline therapy have not been documented in cats. As such, the AHS currently does not recommend the use of doxycycline in heartworm-infected cats.[62] As is the case in dogs, the

AHS recommends that heartworm-infected cats be started on preventives as soon as they are clinically stable. The prognosis for heartworm-infected cats should be considered guarded. Venco, et al. (2008) found that although 27 of 33 (82 percent) naturally infected cats self-cured, six (17 percent) died and four of those showed no clinical signs prior to death.[8] Atkins, et al. (2000) also found that median survival time of cats diagnosed with heartworm disease was 1.5 years.[16] However, if cats survived beyond the day of presentation, this increased to four years.[16]

Surgical extraction of adult worms may be attempted in dogs and cats with caval syndrome. This is accomplished with alligator forceps or an intravascular retrieval snare introduced via the right jugular vein.[32] In cats, surgical extraction of worms can also be attempted via a left thoracotomy and right ventriculotomy.[62] In severely infected dogs, surgical extraction of heartworms may offer comparable efficacy to melarsomine treatment with improved safety.[68] Care should be taken to remove worms intact, especially in cats where accidental damage to worms during extraction can result in acute circulatory collapse and death.[21]

Once a diagnosis of heartworm disease has been made and a treatment plan decided upon, all affected dogs and cats should be started on preventives as soon as they are stable.[32,62] Exercise restriction should begin immediately after diagnosis and should continue until animals are heartworm-free.[32,62] Clinical monitoring will vary depending on the severity of infection but should include regular veterinary examinations and repeated antigen testing; radiography is also useful for monitoring the extent of cardiac and pulmonary pathology. Because macrocyclic lactone preventives reduce the numbers of circulating microfilariae, antigen tests are the most reliable way of monitoring post-treatment worm burdens in dogs.[32,67] Dogs treated with melarsomine should be antigen-negative within six months post-treatment, and dogs treated with alternate adulticidal therapies (*e.g.*, doxycycline and ivermectin or long-term macrocyclic lactone administration) should be tested every four to six months until repeated tests are negative.[32] The AHS recommends that cats be retested at six- to 12-month intervals using both antigen and antibody tests.[62] Once a cat is antigen-negative and clinically normal, however, antibody testing may be optional since test results will be positive after repeat exposure even if the cat is on preventive medication.[62] If infection persists, retreatment may be considered as described above. Retreatment of dogs with melarsomine is potentially very serious, and the AHS recommends that there be a strong expectation of additional benefit before retreatment is undertaken.[32]

PREVENTION

Prevention of canine and feline heartworm disease includes chemoprophylaxis (the regular administration of preventive drugs) and surveillance (regular testing). Even though heartworm is mosquito-borne, vector control is impractical for the majority of households, hence the focus on chemoprophylaxis and surveillance.

The AHS recommends year-round use of chemoprophylactics that include activity against endo- and/or ectoparasites in all dogs and in cats living in heartworm-endemic areas.[32,62] Although heartworm transmission may not occur year-round in all areas, year-round use of a broad-spectrum antiparasitic drug effective against other parasites such as fleas, ticks and intestinal worms, may improve compliance by making it easier to remember a consistent dosing schedule and by integrating with other parasite prevention schedules.[62] The retroactive efficacy of macrocyclic lactones on older larvae and mature heartworms also means that year-round administration of chemoprophylactics provides a safeguard in case of a missed dose.[63-65] The AHS recommends that dogs be started on heartworm preventives by 8 weeks of age.[32] Recommended testing protocols vary depending on the age (puppy or adult), origin (owned or shelter) and prevention status (currently on preventives, missed doses, changing products, unknown history)

of individual patients.[32,69] Annual surveillance using an antigen test is recommended for all dogs, with additional testing sometimes necessary depending on the dog's history.[32] Antigen tests are recommended, as long-term administration of macrocyclic lactones can result in false-negative microfilaria tests.[64-66] The recommended approach to routine chemoprophylaxis and testing is outlined in *Table 3*. The approach to testing will vary in heartworm-infected dogs, as discussed in the treatment section on page 7. The AHS considers routine testing of cats to be optional; testing using antigen and antibody tests can help to inform veterinarians and owners of the cat's risk of being infected or of developing HARD and can help to reinforce the need for chemoprophylaxis.[62] However, veterinarians must be aware of the limitations of these tests. The primary reasons for testing cats are to gather supporting evidence when heartworm infection is suspected, to monitor the clinical course of disease in heartworm-infected cats and to establish a baseline prior to commencing chemoprophylaxis.[62]

Drugs available for the prevention of heartworm infections in dogs and cats are the macrocyclic lactones ivermectin, milbemycin oxime, moxidectin and selamectin.[32,62] They have wide safety margins, are active against microfilariae, L3 and L4 larvae and some have activity against adult worms if used continuously for long periods.[32,63-65] As illustrated in *Table 4,* page 12, some are combined with other drugs such as imidacloprid, pyrantel or lufenuron in order to extend their spectrum of activity against other endo- and ectoparasites, and products are available for both dogs and cats. Products are formulated for administration orally, by topical application or subcutaneous injection.[32] Collies and other dogs deficient in the p-glycoprotein gene may be at an increased risk of adverse reaction to macrocyclic lactones, especially if livestock formulations are used

Table 3: Approach to Heartworm Prevention and Testing in Dogs

Patient	Situation	Prophylaxis	Testing
Puppy	0 – 8 weeks of age	Begin by 8 weeks of age	Annual
	8 weeks – 6 months of age, not on preventive	Begin	Optional test 6 months after starting chemoprophylaxis; annual thereafter.
	Over 6 months of age, not on preventive	Begin	Immediately. Optional re-test in 6 months if initial test negative; annual thereafter.
Dog on heartworm preventive	Current, continuing	Continue	Annual
	Missed dose(s) with ‹ 6 month gap	Restart	Optional at restart and again in 6 months; annual thereafter.
	Changing preventive product	Continue	Immediately. Optional re-test in 6 months if initial test negative; annual thereafter.
Dog not on heartworm preventive	Shelter or unknown origin, missed doses for › 6 months, preventive history unknown, no history of preventive use	Begin	Immediately. Then re-test in 6 months; annual thereafter.

Adapted from Rubin, et al. 2010, and Colby, et al. 2011.

Table 4: Drugs Available for Heartworm Chemoprophylaxis

A + sign indicates activity against other parasites in both cats and dogs. A # sign indicates activity against these in cats, but not in dogs.
Note: The infective species of hookworm, roundworm and whipworm differ between dogs and cats.

Product	Mode of administration	For cats /dogs	Fleas	Ticks	Hookworm	Roundworm	Whipworm	Tapeworm	Ear mite
Ivermectin	Oral	Cats							
Ivermectin & pyrantel	Oral	Dogs			+	+			
Ivermectin, pyrantel and praziquantel	Oral	Dogs			+	+		+	
Milbemycin oxime	Oral	Dogs			+	+	+		
Milbemycin oxime & praziquantel	Oral	Dogs & cats			+	+	+ (not in cats)	+	
Milbemycin oxime & lufenuron	Oral	Dogs	+		+	+	+		
Selamectin	Topical	Dogs & cats	+	+ (not in cats)	#	#			+
Moxidectin & imidacloprid	Topical	Dogs & cats	+		+	+	+		#
Moxidectin	Injectable	Dogs			+				

Adapted with permission from the American Heartworm Society, www.heartwormsociety.org and *Plumb's Veterinary Drug Handbook*, 6th ed. 2008.

off-label and the dose is miscalculated.[32,70] However, the AHS advises that all products formulated specifically for companion animals are safe when used according to the manufacturers' recommendations.[32]

Lack of compliance is the greatest barrier to the success of heartworm preventive efforts and education is the key to compliance.[32,71,72] Rohrbach, et al. (2010) found that dog owners cited the failure of chemophrophylactics in preventing heartworm as the major obstacle to administration of heartworm preventives, indicating a perceived lack of efficacy.[71] However, Hartogensis (2005) investigated 5,794 claims of heartworm infection in dogs receiving preventives and found that 22 percent (1,301) were related to product failure.[73] Thus, it can be inferred that up to 78 percent of lack of efficacy claims may be related to a lack of compliance.[71] Rohrbach, et al. (2011) also found a widespread lack of knowledge among survey respondents on topics including when to start heartworm prevention in puppies, whether cats are susceptible to infection and whether prophylactic drugs kill adult worms.[71] Respondents' knowledge of testing was similarly varied, with misconceptions about test sensitivity, a lower perceived importance of annual testing and a lack of understanding about the appropriate timing of heartworm tests.[71]

The use of heartworm preventives tends to be seasonal, with increased usage coinciding with the transmission season.[72] Gates and Nolan (2010) estimated that 74–79 percent of dogs and 12–38 percent of cats were receiving heartworm preventives at any given time, however they estimated that 50 percent of dogs or less received chemoprophylactics year-round.[72] Given the reported variability in the level of understanding

of the necessity and timing of preventives, the AHS recommends year-round chemoprophylaxis.[32,71] Appropriate chemoprophylaxis and surveillance is also important in pets obtained from shelters. The level of understanding of heartworm biology and the importance of prevention varies between shelters, as does the frequency of testing, the provision of preventive medications and the approach to treatment or euthanasia of heartworm-infected dogs.[69] Shelters face a number of challenges in the prevention of heartworm in animals in their care; limited-admission shelters and foster programs are generally more likely to provide heartworm testing and prophylaxis, but cost is a major barrier to their provision.[69] Since shelters often have insufficient resources to identify, treat and prevent heartworm infection, it is important that pets obtained from shelters be started on preventive medications and tested according to AHS recommendations.[32,69]

A lack of client compliance is not the only barrier to effective heartworm prevention. Veterinarians often do not question clients about heartworm prevention; Gates and Nolan also found that veterinarians collected information on heartworm, flea, or tick preventative use in only 13–23 percent of patients during routine medical history taking.[72] Veterinarians may overestimate their clients' compliance as well. A survey by the American Animal Hospital Association found that the hospitals surveyed estimated that on average, 70 percent of patients were receiving heartworm chemoprophylactics. In contrast, it was calculated that only 48 percent of all patients seen at the surveyed hospitals were receiving chemoprophylactics.[74] Although these figures are not ideal, it must be recognized that it is not always possible to discuss heartworm prevention with clients. The standard veterinary consultation presents only a limited window of time and the patient's medical problems or client's needs may take priority. However, knowledge of heartworm biology and testing protocols along with an awareness of potential barriers to compliance can help to minimize the gap. For example, New, et al. (1997) found that the efficacy of heartworm preventives against other parasites was important to clients.[75] However, 38 percent of clients who purchased heartworm preventives were unaware that the products had efficacy against intestinal parasites.[75] Gates and Nolan suggested that referring to heartworm preventives as "parasite preventives" might help to close this knowledge gap by emphasizing the products' broad spectrum of efficacy.[72]

CONCLUSIONS

Canine and feline heartworm disease presents a unique diagnostic, therapeutic and preventive challenge to veterinarians. The prevalence of *D. immitis*, the causative agent, varies widely among different geographic regions, which affects the performance of diagnostic tests and the perceived importance of the disease to both veterinary practitioners and clients.[4,59,71,72] Dogs and cats also vary in their susceptibility and response to infection, which further complicates clinical management.[6] Despite these variations in prevalence and susceptibility, the consequences of heartworm infection are serious. Hence, the AHS recommends year-round chemoprophylaxis of all dogs nationwide and all cats in heartworm-endemic areas.[32,62] A variety of products are available for heartworm chemoprophylaxis; many are also effective against other endo- and ectoparasites. When used in accordance with the manufacturers' directions, all products formulated specifically for companion animals are safe.[32] Because a lack of compliance is the greatest barrier to effective prevention, an understanding of heartworm biology and familiarity with the protocols recommended by the AHS, coupled with open and effective client communication, is especially important.

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