

Emerging issues in heartworm disease

DVMs face emerging problems and issues with the development of newer drugs, diagnostic methods and pet-owner awareness

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Canine and feline heartworm diagnostic methodologies as well as treatment and prevention strategies have changed considerably during the previous decade. We have experienced an unprecedented increase in numbers and kinds of available medications and diagnostic aids, and the capabilities of pet owners to acquire information of both a technical and lay nature. This can be both beneficial and detrimental in our efforts to establish and maintain effective strategies for controlling heartworm infections.

Beneficial because pet owners have become more aware of the potential dangers of heartworm infections and because available treatment and prevention products have become more effective and convenient to use. Detrimental because much misinformation can be communicated through e-mail and Web sites dealing with heartworm. Additionally, the activities of newer avermectins and milbemycins against microfilariae and larval heartworms, and even demonstrated activity under certain circumstances against adult stages of heartworms, add additional possibilities to veterinarians' choices in developing and implementing control strategies. The same can be said for immuno-diagnostic assays

now available for in clinic use. Possible discrepancies between traditional methods such as microfilariae detection and antigen or antibody test results can lead to some confusion regarding the actual infection status of certain pets. In this article, I will briefly discuss some of these issues. My purpose is to draw attention to these emerging issues so that veterinarians can better deal with problems that result from them. I also will discuss human heartworm infections. Little has been written about this uncommon, but important, issue.

■ Diagnostic challenges confronting veterinarians

Widespread use of macrolide heartworm preventatives such as ivermectin, milbemycin oxime, moxidectin and selamectin (see Table 1, p. 49) has had a profound effect on the numbers of heartworm-infected dogs seen by veterinarians. Reductions in the number cases of clinical canine heartworm infections are even more dramatic. The excellent efficacies of the medications, together with the convenience of monthly or semi-annual administration has almost eliminated heartworm infection in some areas — or so it seems (see Photo 1).

With these enhanced efficacies come some additional problems. Failure to administer these medications regularly or at appropriate doses can result in heartworm infections. However, these infections gen-

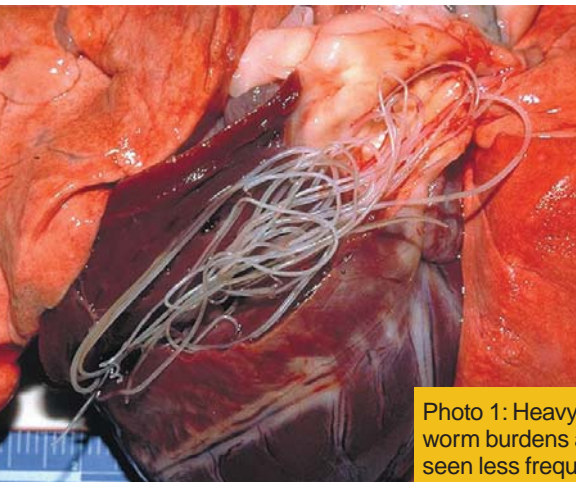


Photo 1: Heavy worm burdens are seen less frequently in heartworm infected dogs because of the widespread use of preventatives.

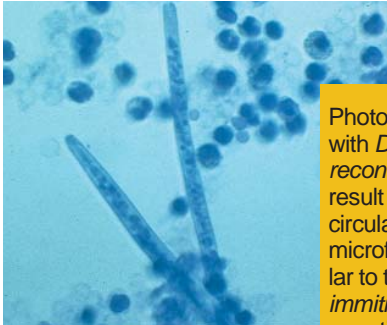


Photo 2: Infections with *Dipetalonema reconditum* (right) result in detectable circulating microfilariae similar to those of *D. immitis* (left) but a negative heartworm antigen test.

erally involve fewer numbers of worms — sometimes too few worms to detect. Fewer worms also mean an increased possibility of single-sex infections and failure of worms to produce detectable microfilariae. We also now know that the macrolide preventatives will, to varying degrees, reduce or eliminate circulating microfilariae from infected dogs (see Photo 2). Consequently, detection of microfilariae no longer can be considered as reliable a means of diagnosis as it once was.

Although point-of-care heartworm antigen tests have become increasingly sensitive and rigorously specific, the lower worm burdens likely to occur in infected dogs seen by veterinarians can even challenge the performance capabilities of these tests. Other phenomena such as fluctuating antigen levels and potentially conflicting antigen, antibody (for feline tests) and microfilariae test results can create diagnostic dilemmas for the veterinarian (see Table 2, p. 51). Currently marketed antigen tests are virtually 100 percent specific for heartworm. Specificity is a more important test attribute than sensitivity, since most of the dogs in any region are negative. A test with limited specificity would result in a significant number of false-positive dogs. These dogs would then be treated unnecessarily with an organoarsenical compound.

Reduced sensitivity might fail to detect dogs with low worm burdens (false negatives - a possible occurrence anyway; see Table 2). These dogs are less likely than dogs with high worm burdens to develop severe heartworm disease. Research has shown that currently marketed tests do differ somewhat in their sensitivities, particularly in dogs with low worm burdens. However, for reasons explained above, it is perhaps more important for veterinarians to base selection of point-of-care heart-

worm tests on test attributes other than sensitivity and specificity. Examples of other attributes include:

- 1) need to process single vs. multiple simultaneous samples (batching);
- 2) ease of conduct of the test (i.e. number of steps, reagents, etc.);
- 3) ease of visualization of results (brightness of line or dot, or liquid color change);
- 4) time required to conduct the test;
- 5) cost per test.

Most of the immuno-ELISA and immuno-chromatographic tests that are currently marketed would score well when these criteria are applied to them. An understanding of situations that today's diagnosis and prevention environments can create is essential if veterinarians are to use

these excellent products and diagnostic aids to their full potential.

Emerging issues in treating heartworm infections

For many years, the only adulticidal organoarsenical compound available to veterinarians was thiacetarsamide sodium. The approval and marketing of melarsomine dihydrochloride led to the eventual disappearance of thiacetarsamide from the marketplace. Melarsomine provides the veterinarian with a product with improved efficacy, safety and ease of administration compared to its predecessor. Melarsomine was introduced with a unique flexible dosing regimen that was correlated to the clinical condition of the heartworm-infected dog.

Dogs that are asymptomatic or in the

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Table 1: Selected heartworm preventatives approved for use in dogs or cats.

Anthelmintic(s)	Proprietary Name	Regimen (Formulation)	Target Pet Animal	Target Parasites†
Diethylcarbamazine/Oxibendazole	Filaribits Plus® (Pfizer)	Daily (Flavored tablet)	Dog	DI,TC,AC,TV
Ivermectin	HeartGard® Tablets (Merial)	Monthly (Tablet)	Dog	DI
	HeartGard® Chewables (Merial)	Monthly (Chewable)	Dog	DI
	HeartGard® for Cats (Merial) Monthly	Monthly (Chewable)	Cat	DI,AT,AB
Ivermectin Pyrantel Pamoate	HeartGard® Plus Chewables (Merial)	Monthly (Chewable)	Dog	DI,TC,TL,AC,AB,US
Milbemycin Oxime	Interceptor® Flavor Tabs® (Novartis)	Monthly (Flavored Tablet)	Dog Cat	DI,TC,TL,AC,TV DI, Tca, AT
	Sentinel™§ (Novartis)	Monthly (Flavored Tablet)	Dog	DI,TC,TL,AC,TV
Moxidectin	ProHeart® (Fort Dodge)	Monthly (Tablet)	Dog	DI
	ProHeart® 6 (Fort Dodge)	Every 6 months (Sustained release subcutaneous injectable containing 10% moxidectin microspheres)	Dog	DI,AC
Selamectin	Revolution™¶ (Pfizer)	Monthly (Topical solution)	Dog Cat	DI, DI,Tca,AT

†TC=Toxocara canis, Tca=Toxocara cati, TL=Toxascaris leonina, AC=Ancylostoma caninum, AB=Ancylostoma braziliense, AT=Ancylostoma tubaeforme, US=Uncinaria stenocephala, TV=Trichuris vulpis, DI=Dirofilaria immitis.
 Note: Prevention, treatment or control claims vary; see labels for specific product claims.
 §Also contains lufenuron for flea control; ¶Also effective against fleas and certain ticks and parasitic mites.

early symptomatic stages of heartworm disease are given a standard two-dose regimen, with 24 hours intervening between each dose. Dogs with late stage heartworm disease (class III disease) can be given a single dose of melarsomine and subsequently released to the owners care and vigilance at home. The dog is returned one month later to receive the standard two-dose regimen. The rationale for the three-dose regimen is that a partial kill of the adult worms following the single treatment and the dog's subsequent recuperation prior to the full regimen a month later would impose less stress and potential for serious post-treatment thromboembolic disease. The safety appeal of the flexible dosing regimen has led many veterinarians to adopt this regimen as their only treatment protocol. Although this reasoning seems logical when devising therapeutic adulticidal protocols, veterinarians must also remember that the flexible dosing regimen increases the period of time that dogs must be confined since worms are killed over two treatment periods. In addition, the pet owner must bear the cost of an additional treatment and must be responsible enough to return for all scheduled treatments. It is my opinion that melarsomine should be used as its label indicates - the standard two-dose protocol for all but the most seriously diseased

animals, for which the flexible regimen was designed.

Another inevitable consequence of the improved product performance of melarsomine is increased cost. In this case, it is undeniable that the excellent properties of melarsomine are well worth the increase in price. The cost of melarsomine therapy, particularly in large dogs, has resulted in some hesitation by pet owners in some markets to pursue adulticidal therapy. This and other issues such as how to deal with heart-

worm-infected geriatric patients, or patients suffering from other terminal conditions, has resulted in veterinarians considering other adulticidal options.

The most popular of these options has been the exploitation of the slow adulticidal effects of the macrolide endecticide preventatives (i.e. ivermectin, milbemycin oxime, moxidectin and selamectin). Research has shown that most of the macrolide preventatives that are on the market possess some exploitable slow adulticidal properties. These adulticidal properties are best characterized for ivermectin. For example, if dogs harboring adult worms are given ivermectin using the dose band regimen (minimum target: dose 6 ug/kg) at monthly intervals for 16 months, many of the heartworms will die during the regimen. Many of the remaining worms appear structurally abnormal and will likely die.

The stated attributes of this approach to killing adult worms is that worms are killed slowly which will result in less insult to the lungs as the worms are eliminated. Such a result does sound appealing, since dogs must be protected from future infection using this same regimen anyway. It is also substantially less expensive than removal of adult worms using melarsomine. However, it is important to note that the

adult worms can induce a proliferative endarteritis in the cardiopulmonary vessels

in which they are found, and the longer they are left in those vessels, the more severe that reaction is likely to become. It is also notable that the chronic effects of slow worm death have been the subject of a very limited amount of research. At this point it seems that the best advice is to recommend the use of melarsomine when adult infections are detected. If the use of the approved adulticide is refused, then the use of macrolide preventatives in heartworm positive dogs, although investigative, could be justified.

To date, 118 cases of human pulmonary dirofilariasis have been reported in the United States.

■ Feline heartworm infection: Thoughts and strategies

Although heartworm infection in cats was first reported in 1921, many pet owners and some veterinarians either remain unaware or do not believe that heartworms can cause serious and sometimes fatal disease in cats. Most of us are with familiar the potential consequences of heartworm infections in dogs, but we fail to recognize that heartworm in cats differs somewhat from dogs, and that this parasite induces a significantly different clinical response when present in cats. Although the prevalence of heartworm infection in cats has been studied, unique features of feline infections make the true prevalence of feline heartworm difficult if not impossible to assess. A variety of techniques including radiography/angiography, ultrasonography and necropsy, as well as microfilariae, antibody and antigen detection have been used to diagnose and determine prevalence of feline heartworm infection. Not only does use of these different tests make comparison of the different studies difficult, it is important to remember that some of these tests were developed for dogs or were applied to the study of feline prevalences based on guidelines for their use in dogs. Most

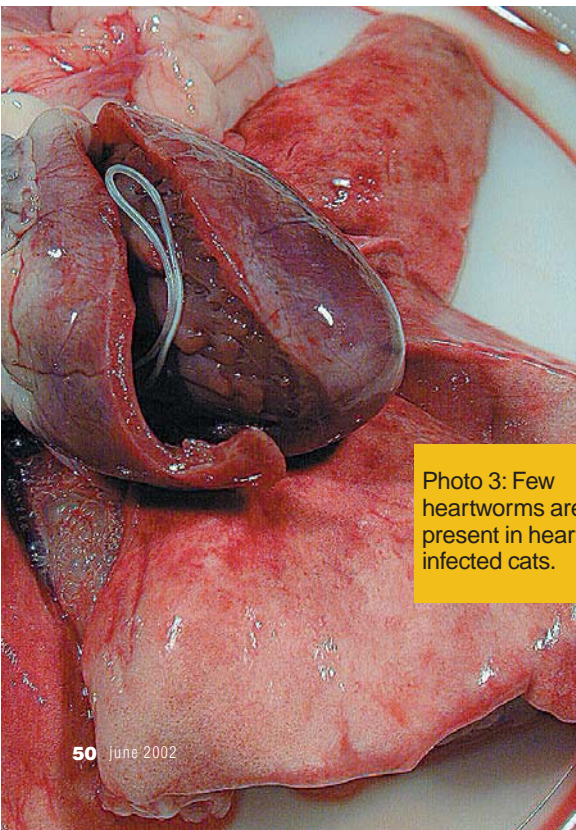


Photo 3: Few heartworms are usually present in heartworm infected cats.

heartworm experts agree that results of published studies indicate that exposure to heartworm infected mosquitoes in cats is surprisingly high, and that the risk of feline heartworm infection remains a concern in many regions of the country.

Most cats infected with heartworm are asymptomatic. However, it is impossible to predict when and under what conditions asymptomatic cats will develop clinical heartworm disease. Cats with clinical heartworm disease present with respiratory signs such as coughing and/or dyspnea, or intermittent vomiting which according to the pet owner is not associated with eating. Some cats also have signs of weight loss and or diarrhea without respiratory signs. Respiratory signs are similar to those observed with

feline asthma. Consequently, feline heartworm disease must be differentiated from asthma. A small percentage of cats exhibit acute respiratory distress and may die suddenly. This peracute presentation also mimics signs of feline asthma or cardiomyopathy (dyspnea). Many of these cats are clinically normal prior to the acute heartworm-induced event.

Diagnosis of feline heartworm infection is based on history, clinical signs and ancillary diagnostic aids already mentioned. Both antigen and antibody tests are available and approved for use in cats. While detection of adult heartworm antigen in cats is confirmation of infection, it is important to remember the lower worm burdens and increased likelihood of all-male infections in

cats make available antigen tests less sensitive (see Photo 3, p. 50). A positive antibody test might result from one of several situations including current adult infection, recently cleared adult infections, ectopic infections, exposed cats on a heartworm preventative or simply exposure to heartworm from infected mosquitoes. These results cannot be used independent of other tests or data to confirm adult infections of the heart or lungs. Because infected cats do not commonly demonstrate circulating microfilariae, standard microfilariae detection assays also cannot be used reliably to confirm infections. Studies also indicate that clinical signs do not correlate with positive serological test results, further substantiat-

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Table 2: Possible causes or explanations for observed heartworm test results in dogs and cats.

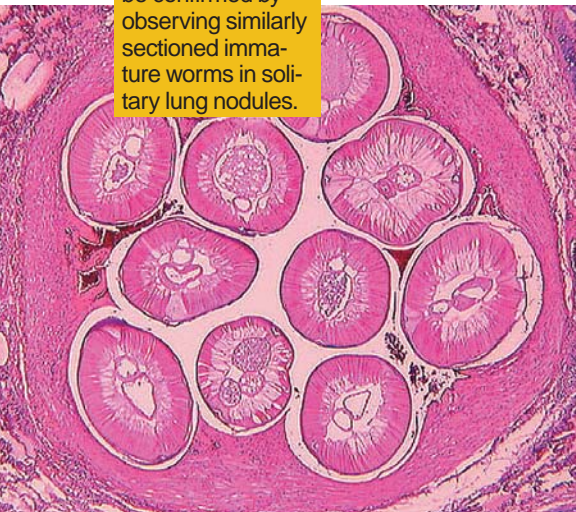
Antigen Test*	Antibody Test**	Microfilariae Test	Possible Cause/Explanation
Canine			
Positive	NA**	Negative	<ul style="list-style-type: none"> ■ Failure to use a microfilaria concentration test could result in false negative if numbers of circulating microfilaria are low. ■ Maturing adult female worms are detectable with antigen test prior to production of microfilaria (uncommon). ■ Dog may have been treated with a microfilaricide, but not with an adulticide. ■ Dog may be receiving or may have received heartworm preventatives that eliminated microfilaria but not adult worms. ■ Dog may be true natural occult [single-sex (female-only) infection; immune-mediated clearance of microfilaria].
Negative	NA	Positive	<ul style="list-style-type: none"> ■ Microfilaria are those of another species such as <i>Dipetalonema reconditum</i> or <i>Dirofilaria</i> spp. other than <i>D. immitis</i> (usually few in number). ■ Microfilaria were acquired from the dam via the placenta (usually few in number and usually seen in young dogs). ■ Adults were removed or have died, but microfilaria persist. ■ Contamination of test materials with microfilariae from a previous positive sample.
Variable§	NA	Negative or positive	<ul style="list-style-type: none"> ■ Fluctuating antigen level usually due to few female worms or age of worms (detection may vary from test to test). Presence or absence of circulating microfilaria could depend on age of female worms, numbers of circulating microfilaria and method of detection and type and frequency of use of preventatives, and host immune responses
Feline			
Negative	Positive	Negative	<ul style="list-style-type: none"> ■ Most common result. Usually due to exposure but failure of larvae to reach maturity. ■ Could be due to low adult worm burden. Cats are usually transiently microfilaremic (due to immune mechanisms) or harbor too few microfilaria to detect. Some tests conducted by reference laboratories may be capable of clarifying infection status. ■ Could be due to elimination of migrating larvae by preventative. However, larvae survived long enough to induce antibody response. ■ Could be due to presence of heartworms at aberrant (ectopic) sites.
Positive	Negative	Negative	<ul style="list-style-type: none"> ■ Uncommon for antibody test to be negative. Rarely, cats do not produce antibody, even when detectable adult worms are present.
Negative	Positive	Positive	<ul style="list-style-type: none"> ■ Uncommon. Too few adult female worms to detect. Cat was examined during brief microfilaremic phase.
<p>*Results of point-of-care tests. Some tests conducted by reference laboratories may provide more definitive results. **Not applicable: antibody tests not used routinely in dogs. §Positive at one time; negative at another or positive with one test and negative with another test. This situation also might be encountered when dogs or cats are tested by two different veterinarians.</p>			

ing the difficulty of diagnosis. Consequently, diagnosis of feline heartworm infection remains a challenge that requires multiple approaches including collection of adequate historical information and/or immunological testing, imaging and perhaps additional hematological tests.

The decision to recommend prevention to clients whose cats might be exposed to heartworms is a controversial one. It is important to make three points about feline heartworm infections to clients that are indecisive about feline heartworm prophylaxis. First, clients should be told that feline heartworm infections are difficult to diagnose. The points made in this discussion can be used to support this statement. Second, feline heartworm disease is not easily or safely treated, nor are there approved or safe medications for removal of adult heartworms from cats. Third, and perhaps most important, clients should be informed that there are safe, effective and approved heartworm preventative medications available for cats (see Table 1, p. 49). In addition, these

medications also are effective against other important internal and external parasites. It is essential that veterinarians inform and instruct pet owners about

Photo 4: Cross section of heartworms in a pulmonary vessel. Human pulmonary dirofilariasis can be confirmed by observing similarly sectioned immature worms in solitary lung nodules.



risks of exposure to heartworm-infected mosquitoes and about the availability of approved preventive medications. In that way, pet owners can make informed decisions concerning the most appropriate course of action for them and their pet.

Human heartworm infections: An emerging zoonosis?

Many veterinarians and pet owners are not aware that humans can be infected with *Dirofilaria* spp. Humans, however, are aberrant hosts and do not usually harbor adult worms or circulating microfilariae. These worms usually die either in the subcutaneous tissues or pulmonary vessels before they mature to adult worms. At these sites, the dead or dying worms usually evoke a demonstrable granulomatous response. Most human infections with *D. immitis* manifest as pulmonary nodules. Other sites of infection with *D. immitis* or *D. immitis*-like worms include the eye, testicle, subcutaneous tissues, urinary bladder, porta caval shunt and peritoneal cavity. Human pulmonary infection results when infective larvae introduced by mosquitoes cannot complete their maturation in the cardiopulmonary vasculature. The heartworm larvae die and subsequently pass to the lungs where the release of antigens and inflammatory mediators lead to endarteritis, pulmonary infarction and nodule formation.

Nodules usually are 1-3 cm in diameter, well-circumscribed, spherical, grayish-yellow and contain a necrotic core. If worms are present, they can be identified by their cross-sectional morphology (see Photo 4). Identification usually requires submission of the specimen to an expert laboratory.

Most cases are asymptomatic, thus the condition is likely under reported. Generally, it is misdiagnosed as carcinoma or metastatic disease. Surgical resection has been the treatment of choice. As we would expect, the frequency and distribution of human pulmonary dirofilariasis is associated directly with the prevalence and distribution of canine heartworm infections. The greatest numbers of human cases occur in the Atlantic, Gulf Coast and Mississippi valley regions — areas where prevalences of canine heartworm infections are highest. To date, 118 cases of human pulmonary dirofilariasis have been reported in the United States. Thirty-seven of these cases have been reported since 1990. Infected persons ranged in age from 28-79 with most reported patients in the fifth or sixth decade of life. The majority of infections occur in white males,

although all races and both sexes appear susceptible.

Although uncommon, human pulmonary dirofilariasis appears to be an emerging zoonosis. Increased awareness by the medical community and advances in early diagnosis have resulted in increased detection rates. Although impossible to eliminate entirely, increased emphasis on canine heartworm prevention could reduce the prevalence of heartworm infected mosquitoes in heartworm endemic areas. This aspect of prevention rests with the veterinarian and pet owner. **DVM**



Dr. Blagburn holds the appointment of Distinguished University Professor at the Auburn University College of Veterinary Medicine. He received his doctorate in parasitology from the

University of Illinois College of Veterinary Medicine. A significant portion of Dr. Blagburn's research effort is dedicated to collaborative development of new pharmaceuticals directed against parasites and parasitic diseases. He is currently an associate editor for the Journal of Parasitology. He currently serves on the editorial board of Veterinary Therapeutics and is the author of more than 190 publications.

Suggested reading

- Shah MK: Human Pulmonary Dirofilariasis. 1999, Southern Medical Journal vol 92, pp. 276-279.
- Recent Advances in Heartworm Disease: Symposium '01. American Heartworm Society, Batavia, IL, 2002, In Press.
- Rew R and J Vercruyssen (eds). Macrocylic Lactones in Antiparasitic Therapy. Oxford University Press, NY, (ISBN 0851996175), 2002, In Press.
- Knight, DH. Review and Update of American Heartworm Society Recommendations for Diagnosis, Treatment, and Prevention of Heartworms in Dogs and Cats. Proceeding of the North American Veterinary Conference 2002, Small Animal - Parasitology, pp.613-619.