

# **Changing Trends and Issues in Canine and Feline Heartworm Infections**

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Canine and feline heartworm diagnostic, treatment and prevention strategies have changed during the previous decade. We experienced an unprecedented increase in the numbers and kinds of available medications and diagnostic aids, and also in the capabilities of pet owners to acquire information. This can be both beneficial and detrimental in our efforts to establish and maintain effective strategies for controlling heartworm infections. Pet owners have become more aware of the potential dangers of heartworm infections. Also, available treatment and prevention products have become more effective and convenient to use. However, much misinformation is communicated through electronic mail and web sites dealing with heartworm. The activities of newer avermectins and milbemycins against microfilaria and larval heartworms, and activity of some against adult stages of heartworms, add additional possibilities for heartworm control. The same can be said for immunologic tests for in clinic use. Discrepancies between microfilaria tests and antigen or antibody test results can lead to confusion about the actual infection status of pets. In the following, I will discuss some of these issues. My purpose is to draw attention to these issues so that veterinarians can better deal with problems that they create.

## **Diagnostic challenges confronting veterinarians**

Wide spread use of macrolide heartworm preventatives such as ivermectin, milbemycin oxime, moxidectin, and selamectin 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 is even more dramatic. The excellent efficacies of the medications, together with the convenience of monthly administration has almost eliminated heartworm infection in some areas - or so it seems. 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 generally 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 microfilaria. We also now know that the macrolide preventatives will, to varying degrees, reduce or eliminate circulating microfilaria from infected dogs. Consequently, detection of microfilaria 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 challenge the capabilities of these tests. Other phenomena such as fluctuating antigen levels and potentially conflicting antigen test results, antibody test results (for feline tests) and microfilaria test results can create diagnostic dilemmas for the veterinarian

(table 1). Currently marketed antigen tests approach 100% specificity. Specificity can be 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 1). 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 heartworm 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 and 6) other diagnostic capabilities of tests (i.e. detection of antibodies or antigens to other disease agents). 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 the treatment of 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 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) or dogs with suggestion of high worm burdens (semi-quantitative antigen tests; historically high worm burdens in an area; radiographic lesions suggesting high worm burden [not always definitive]) 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. The flexible dosing regimen is the treatment of choice of the American Heartworm Society, for reasons mentioned above.

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 heartworm-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 (sometimes call “soft kill”) of the macrolide preventatives (i.e. ivermectin, milbemycin oxime, moxidectin and selamectin). These adulticidal properties are best known and characterized for ivermectin/pyrantel pamoate (Heartgard Plus, Merial). 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 one to two years or more, many (in some cases all) of the heartworms will die during the regimen. Remaining worms appear structurally abnormal and will likely die. The prevailing mantra seems to be “the older the worms, the longer they will require to kill”. 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 that 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. Some research suggests that the “soft kill” approach should not be used in active dogs or dogs with presenting signs of heartworm disease. 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 might be justified.

### **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 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 microfilaria, antibody and antigen detection have been used to diagnose and determine prevalence of feline heartworm infection. However, few tests (ultrasonography and antigen detection are possible exceptions) can be used alone to confirm heartworm infections. Most 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 can be similar to those observed with feline asthma. Consequently, feline heartworm disease must be differentiated from other respiratory disease with similar presentations. 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 mentioned above. Both antigen and antibody tests are available and approved for use in cats. While detection of adult heartworm antigen in cats can be a confirmation of infection, it is important to remember that the lower worm burdens and increased likelihood of all-male infections in cats make available antigen tests less sensitive. 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. An increasing number of heartworm-infected cats remain antibody test negative. Infected, antibody-negative cats are difficult to explain and are the subject of much current interest. Because infected cats do not commonly demonstrate circulating microfilaria, standard microfilaria 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 substantiating the difficulty of diagnosis. 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.

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 the above 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. In addition, these medications are also effective against other important internal and external parasites. It is essential that veterinarians inform and instruct pet owners about 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.

### ***Wolbachia*: What is it and what do you need to know?**

*Wolbachia* are intracellular bacteria that infect numerous species of filarial worms including heartworms. Many contend that these friendly inhabitants (endosymbionts) play a role in the pathogenesis of diseases caused by heartworms and other filarids. Contention is that host immune responses directed at *Wolbachia* can actually go awry and enhance the disease process in heartworm infections. Some also contend that elimination of *Wolbachia* spp. from heartworms may affect the survival of adult heartworms and may decrease the host's errant immunologic responses when adult worms are killed or die. Another belief is that since dogs and cats do not harbor *Wolbachia*, certain molecules unique to the bacteria may be used as targets for heartworm

detection. This would be particularly helpful in the cats where, as describe above, worm burdens are often too low to detect with traditional antigen detection methods. However, before we get too optimistic, the life cycle of these bacteria involves several different stages. Susceptibilities of the different stages to anti-infective agents may vary. Certain of the stages may be refractory to treatment (diagnosis?) because of their ability to enter quiescent or resting states.

**REFERENCES AVAILABLE ON REQUEST.**