FOUR UPDATES THAT COULD CHANGE YOUR HEARTWORM STRATEGIES

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To say that canine and feline heartworm diagnostic, treatment and prevention strategies are changing is the archetype of understatement. We are experiencing an extraordinary increase in the numbers and kinds of available preventives and diagnostic tests, and the capability to acquire and apply new information. This can be both beneficial and disadvantageous. Beneficial because pet owners have become more aware of the dangers of heartworm infections. Also, available treatment and prevention products have become more effective and convenient to use. That said, misinformation could be communicated through electronic mail, social media, and web sites dealing with heartworm. It is difficult to separate fact from opinion and to know and understand what is important. Among emerging issues are 1) resistance and its influence on our selection and use of products, 2) antigen blocking and the inclusion of heat and chemical treatment in our diagnostic strategies, 3) selection of treatment strategies and 4) *Wohlbachia* and its function in heartworm infection and disease. All add complexities in dealing with heartworm infection. Discrepancies between microfilaria tests and antigen or antibody test results can lead to confusion regarding the actual infection status of pets. The availability of approved adulticide and experimental "slow-kill strategies provide a landscape of options that can be difficult to navigate. I will discuss some of these issues and try to identify what we know and what is important.

Diagnostic challenges confronting veterinarians

Wide spread use of macrolide heartworm preventives such as ivermectin, milbemycin oxime, moxidectin, and selamectin has had a demonstrable 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 or semi- annual administration has almost eliminated heartworm infection if 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 to produce detectable microfilaria. We also now know that most preventives will, to varying degrees, reduce or eliminate circulating microfilaria from infected dogs. Consequently, detection of microfilaria is no longer as reliable a confirmation 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. In addition, concurrent infections in dogs with other parasites or presence of other diseases, or simply excess heartworm antibody compared to circulating antigen, could affect the detection of heartworm antigen (antigen blocking). Heat or chemical treatment of blocked samples may return a positive result. Currently marketed antigen tests approach 100% specificity. Specificity can be a more important test attribute than sensitivity, since most of the dogs seen by veterinarians 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 organo-arsenical compound. Reduced sensitivity might fail to detect dogs with low worm burdens (false negatives - a possible occurrence anyway). 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 in their sensitivities, particularly in dogs with low worm burdens. In addition to sensitivity and specificity the following should also be considered in test selection: 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 current diagnosis and prevention environments can create is essential if veterinarians are to use these excellent products and diagnostic aids to their full potential. An extensive array of point-of-care (POC) and reference laboratories test are available to veterinarians. I remain a strong supporter of in-clinic heartworm tests. Excellent POC tests include Snap® Heartworm RT, Snap® 4DX Plus, Dirochek®, Witness® Heartworm, VetScan and Solostep®. Many tests are also available through commercial, state and academic laboratories. However, it is essential to inquire about their performance characteristics before deciding on a specific test.

Emerging issues in the prevention and treatment of heartworm infections

Heartworm infection can result in potentially serious and sometimes fatal diseases in both dogs and cats. Fortunately, numerous safe and effective monthly, semi-annual and annual heartworm preventives have been developed and delivered to the market in the last 30 years. All major heartworm preventives belong to the macrocyclic lactone (ML) class of endectocides. Current MLs approved for heartworm prevention in dogs and cats include ivermectin, milbemycin oxime, moxidectin, and selamectin. All approved MLs exert their effects by targeting a group of ligand-gated chloride ion channels unique to invertebrates. The L_3 and L_4 larval stages of *D. immitis* are exceptionally sensitive to the MLs. Recently, it seems that the frequency of lack of heartworm preventive efficacy (LOE) reports for the MLs in dogs has increased. In reality, failure of any of the preventives to prevent heartworm infection in dogs is extremely rare (estimated to be <0.1% - although it may be higher in certain regions). It is now known that certain LOE reports are the result of resistant heartworms. However, other factors such as improved tests, increased frequency of testing, clinic or client compliance, or a combination of these, can contribute to an increase in numbers of heartworm positive dogs.

Melarsomine dihydrochloride (Diroban™, Immiticide®) provides the veterinarian with a product with efficacy, safety and ease of administration when eliminating heartworms. Melarsomine was introduced with a flexible dosing regimen that was correlated to the clinical condition of the heartworm-infected dog and the presumption of worm burden. Dogs that are asymptomatic or in the early symptomatic stages of heartworm disease may be treated with the 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 (approximately 50%) 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 three-dose regimen is also more effective at eliminating adult heartworm. The safety appeal of the flexible dosing regimen has led many veterinarians to adopt this regimen as their only treatment protocol. Veterinarians must remember that the flexible dosing regimen increases the period of time that exercise restriction is required, 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 Companion Animal Parasite Council (CAPC) and the American Heartworm Society (AHS). Treatment to remove adult heartworms is not always 100% effective. A positive heartworm test 7 months or more after treatment can be due to several factors that we will discuss. AHS now recommends the concurrent use of doxycycline (see below) together with placement of dogs on preventive for two or more months prior to initiation of the adulticide regimen. This delay is considered unnecessary by some, given the efficacy of the heartworm preventives and melarsomine dihydrochloride.

Another consequence of the improved 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 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 slow adulticidal effects (often referred to as "slow kill") of the macrolide preventives (i.e. ivermectin, milbemycin oxime, moxidectin and selamectin). These adulticidal properties are best known and characterized for ivermectin/pyrantel pamoate (Heartgard® Plus, Boerhinger Ingelheim). For example, if dogs harboring adult worms are given ivermectin using the dose band regimen (minimum target: dose 6 μg/kg) at monthly intervals for 1.5 to two years or more, many (in some cases most) 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, and the longer that they are left in those vessels, the more severe that reaction is likely to be. It is also notable that the chronic effects of slow worm death have been the subject of a limited amount of research. Some research suggests that the "slow kill" approach should not be used in active dogs or dogs with clinical 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 approved adulticide is refused, then the use of macrolide preventives in heartworm positive dogs might be considered. Recent research indicates that concurrent use of doxycycline (for one month; see dosage and regimen below) and moxidectin (Advantage Multi®; monthly) results in demonstrable efficacy against adult heartworms.

I am asked about the need to remove microfilaria (mff) from heartworm-infected dogs. In the past, several of us have recommended placing microfilaremic dogs on prevention. If adult worms are removed, mff will eventually disappear. I now believe that active removal of mff after the use of melarsomine is necessary for two reasons. Persistent of mff exposed to

heartworm preventives may increase the likelihood of resistance. Second, the continued presence of mff serves as a source of infection for mosquito vectors. We have encountered a few dogs whose mff persist with the repeated use of milbemycin oxime (0.5 mg/kg per os) or high dose ivermectin (50 µg/kg and higher either per os or by subcutaneous injection). These microfilariae were eliminated in some dogs by concurrent use of doxycycline and microfilaricides. With the approval of Advantage Multi® as a microfilaricide, it seems reasonable to take advantage of this claim. Benefits include the support of the product sponsor if adverse events occur or if mff cannot be eliminated.

Interest in mosquito control as an adjunct heartworm preventives is increasing. Mosquito avoidance strategies such as use of screen barriers and restricting outdoor animal activity to times when mosquitoes are not likely to be present can be helpful in preventing heartworm transmission. A more achievable preventive goal is to utilize topical flea/tick products that also have claims against mosquitoes (e.g. Vectra 3D® CEVA).These products prevent mosquito feeding and block uptake of microfilaria and prevent transmission of infective larvae to recipient dogs. Research is now available to support this strategy.

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

Wolbachia pipientis is an intracellular bacterium that infects 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* from heartworms may affect the survival of adult heartworms and microfilariae, the ability of microfilariae to infect and develop within mosquito vectors, and may decrease the host's errant immunologic responses when adult worms are killed or die. At present, there appears to be evidence that pretreatment of heartworm infected dogs with doxycycline at the rate of 20 mg/kg per day (10 mg/kg BID) for one month prior to administration of melarsomine dihydrochloride may decrease the severity post-treatment thromboembolic and immunopathologic events. Data also suggest that administration of doxycycline (together with a microfilaricide) also can aid in the elimination of microfilariae from heartworm infected dogs and can render microfilariae noninfectious to mosquitoes. As mentioned above, concurrent administration of doxycycline and preventive may hasten the death and elimination of adult heartworms in dogs.

References available on request.