Heartworm Disease—Winning or Losing?

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EPIDEMIOLOGY

Dirofilaria immitis infection, or heartworm (HW) disease, is considered endemic in dogs of all US states and territories, except Alaska. Other primary hosts in the *Canis* species include coyotes and wolves, whereas less common hosts include foxes, cats, ferrets, sea lions, and seals. The disease is spread by mosquito vectors, with more than 50 mosquito species capable of transmitting infection. Introduction of new mosquito species and increasing ranges of more established species keeps the threat of HW infection high. One particular species of concern, *Aedes albopictus*, is an urban dwelling mosquito which tends to reproduce in small amounts of water, e.g. flower pots. The recognition of 'heat islands' within or around cities now documents how microenvironments may exist for more or total year-round risk of infection.

LIFE CYCLE

Heartworm infection occurs as mosquitos ingest L1 infective larvae from an infected dog/host. Within a few weeks, these larvae will develop into L3 stages which can be transmitted by the mosquito to naive dogs. Thus L1, L2, and L3 forms are found in the mosquito. The L3 forms transmitted to the dog move through various tissues (becoming L4 and L5 forms), and eventually enter veins where they are transported toward the heart and lungs by 2-4 months post-infection. In the pulmonary arteries and right ventricle, the worms mature from L5 to reproducing adults, releasing new microfilariae into the circulation (6-9 months post-infection). Thus there is a window of time post-infection when antibody, antigen, and/or microfilaria tests can be negative in an infected dog!

PREVENTION

Prevention of heartworm infection should be the goal for owners and veterinarians alike. Prevention failure can result from ignorance on the part of owners as to the presence or potential severity of infection, lack of owner compliance, or from inadequate instruction on preventative measures by the attending veterinarian. Studies of owner compliance indicate probably only 50-60% of owners purchasing HW preventative are administering in a manner that protects their dog from infection.

Macrocyclic Lactone (Macrolide) Antibiotics: The macrocyclic lactone endectocides (macrolides), ivermectin (Heartgard®, Iverhart ®, TriHeart®), ivermectin with pyrantel pamoate (Heartgard® Plus, Iverhart Plus®, TriHeart® Plus), ivermectin with pyranel pamoate and praziquantel (Iverha®rt Max), milbemycin oxime (Interceptor®), milbemycin oxime with lufenuron (Sentinel®) and with spinosad (Trifexis®), selamectin (Revolution™), and moxidectin (ProHeart®, ProHeart® 6), and moxidectin with imidicoprid (Advantage/Multi™) are highly effective and safe heartworm preventatives in a variety of formulations. These agents, interrupt larval development (L3 and L4) during the first 2 months after infection and have a large (reach back) window of efficacy when administered monthly. These products have been considered to have very high efficacy, "virtually 100%, when used as directed". All marketed macrolides are safe in collies when used as directed at preventive dosages (and used alone). They each have microfilaricidal efficacy and they also render female heartworms sterile. Hence microfilarial tests for HW infection cannot be reliably used in dogs receiving these products. Prophylaxis should begin no later than 6 to 8 weeks of age in endemic areas or as soon thereafter as climatic conditions dictate. Macrolides should be administered precisely as indicated by the manufacturer. If accidental lapses of

more than 10 weeks occur, the preventative should be reinstituted at recommended doses and maintained for at least 12 consecutive months. In the event of a lapse in preventative administration during a time of known exposure risk, an antigen test should be performed 7-8 months after the last possible exposure to determine if infection has occurred. It is recommended by the American Heartworm Society (AHS) and the Companion Animal Parasite Council (CAPC) that these agents are used year-around in all areas of the U.S.

Macrocyclic Lactone "Resistance/Tolerance": In 2005, the FDA Center for Veterinary Medicine (FDA-CVM) reported an increase in the reports of LOE (Lack of Effectiveness) for macrocyclic lactones and required that such agents no longer be labelled as "perfect" in terms of efficacy. This failure of complete rapid microfilarial clearing, coupled with concerns in the Mississippi River delta region, has caused concern that resistance to this class of drugs may be developing. The evidence for this is small and contradictory, but taken together, the data argue that microfilariae isolated from a small percentage of dogs in this region have characteristics suggesting tolerance to the drug group.

Recently, a single heartworm isolate (MP3) from north-eastern Georgia has shown resistance/tolerance to some macrocyclic lactones, when administered once, 30 days after heavy experimental challenge. While an important finding, demonstrating the heterogeneity of heartworms in the U.S., this appears to be unrelated to concerns of resistance in the Mississippi River delta region. Nevertheless, all current heartworm preventives belong to the same class of molecule, the macrocyclic lactones, and thus resistance to one is likely to be associated with resistance to all.

Compliance appears to play a much larger role (>95%?) than possible resistance in dogs developing HW infection while on preventive therapy. Excerpts from a joint consensus of the American Heartworm Society (AHS) and CAPC suggest that "*There is evidence in some heartworm populations for genetic variations that are associated with decreased in vitro susceptibility to the macrocyclic lactones. Whether the observed genetic variations constitute heritable resistance is being investigated. Most credible reports of lack of effectiveness, that are not attributable to compliance failure, are geographically limited at this time. The extent of the problem is obscured by demonstrated lack of owner and DVM compliance, possible changes in environmental/vector factors, and more effective antigen testing. The potential for resistance is not a reason to abandon use of approved preventive products*.

THERAPY

Therapy has traditionally been directed toward adult HWs first, and microfilariae second, due to the arteritis and associated pulmonary disease induced by adult HWs. The impact of adulticide therapy however was potentially life-threatening to heavily infected dogs. The time-honored approach involved adulticide followed in 3-6 weeks by macrolide therapy to rid the patient of microfilariae. In 2-3 weeks, a second microfilaria concentration test is performed and, if negative, preventative started. If still positive, the treatment is repeated or alternatively, chemoprophylaxis begun (assuming that no adverse reaction occurred on the initial treatment). Persistent antigenemia (after 6-7 months) indicates continued patent infection. The evolving current mindset however is to reduce the overall *D. immitis* burden through a slower initial process.

Microfilaricide first: An alternative approach is to begin the administration of a macrolide preventative at the time of diagnosis, often days to weeks prior to adulticidal therapy. If the dog is microfilaremic, particularly with high numbers, pretreatment with corticosteroids and Benadryl may be warranted. If this approach is used, the dog must be rendered microfilariae-free by 1-3 months post-diagnosis.

Recent evidence demonstrates that an intracellular gram-negative bacteria, *Wohlbachia*, lives in microfilariae and adult HW in a symbiotic relationship. Death of the *Dirofilaria* forms releases dead *Wohlbachia* bacteria, inciting an inflammatory (often acute) response. *Wohlbachia* is sensitive to doxycycline, and doxycycline therapy (10 mg/kg BID) alone rapidly eliminates the intracellular bacteria, resulting in the demise of some *Dirofilaria* forms too. Coupling these pharmacologic properties together, the concurrent usage of a macrolide and doxycycline reduces microfilarial numbers more rapidly than use of a macrolide alone; and dogs become microfilaria-negative in less than 3 months.

Adulticidal therapy

The adulticide melarsomine is an organoarsenical superior in safety and efficacy to thiacetarsemide. This product, which is administered twice at 2.5 mg/kg q24h, has a mean retention time 5 times longer than thiacetarsemide and its metabolites are free in the plasma, on which HW feed. With 2 doses, the efficacy is over 90% (FDA study) with a 50% worm kill with 1 dose. This then allows "split-dose" protocol to be utilized in severely afflicted individuals or in those in which pulmonary thromboembolism (PTE) is a concern. This method results in destruction of only one-half the worms initially (1 IM injection of 2.5 mg/kg), thereby lessening the chance for embolic complications. This single dosage is followed by a 2 dose regimen in 1-3 months, if clinical conditions permit. Several parasitologists recommend this 3 dose regimen in all HW cases unless there is financial constraint or underlying concern for arsenical toxicity (for example, preexistent severe renal or hepatic disease). One disadvantage to the "split-dose" method, in addition to the expense, is the need for 2 months' exercise restriction.

The most common complication to melarsomine therapy is the local inflammatory reaction at the injection site. This can be minimized by following the manufacturer's directions explicitly (change needles before injecting, choose deep IM site with care, put pressure on site after injection, and alternate sites). In addition, corticosteroids (e.g. dexamethasone) or NSAIDs can be given at the time melarsomine is administered to lessen the reaction.

An Alternative? "Soft" or "Slow" Kill without a targeted adulticide

Certain macrolides do have adulticidal properties. Ivermectin, when administered for 31 months continuously has ~95% efficacy in alleviating young heartworm infections. Selamectin and moxidectin also appear to have some adulticidal efficacy. Recent data suggests that an aggressive macrolide protocol (ivermectin, given at preventive dosages weekly or every 2 weeks, instead of monthly), coupled with a regimen of doxycycline will hasten worm destruction, with worm eradication with approximately 9 months' therapy. Furthermore, microfilariae are eradicated more quickly in this manner. The AHS advocates, when melarsomine is unavailable, using preventive monthly and doxycycline at 10 mg/kg BID one month on, two months off, etc, until the patient reverts to an antigen-negative status. While there may be a role for this "slow kill" therapeutic strategy in cases in which patient age, financial constraints or concurrent medical problems prohibit melarsomine therapy, the current AHS recommendations are that **macrolide therapy <u>not</u> be adapted as the primary adulticidal approach.**

SUMMARY

Changes in HW treatment protocols, using a macrolide and doxycycline before melarsomine, have moved us toward a slower *Dirofilaria* kill and safer treatment options for infected dogs. Increasing failures in owner compliance in HW prevention, however, can result in losing the battle to prevent heartworm infection.

Reference: http://www.heartwormsociety.org/veterinary-resources/canine-guidelines.html