Canine Heartworm: A Review of the Basics

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Dirofilaria immitis, also known as canine heartworm, is arguably the most important parasite of dogs in North America. Heartworm has a worldwide distribution, but as a general rule is most severe in tropical and warm/humid areas of the world. As of 2010, heartworm-positive dogs had been reported in every state in the continental United States. Due to the large number of dogs that are diagnosed every year, and the resulting expense of treatment, this disease is of huge economic importance. In fact, millions of dollars are spent on heartworm prevention, diagnosis and treatment each year. Because of the endemic nature of heartworm, and the expense of treatment, it is imperative that everyone, even those in historically non-endemic regions, be knowledgeable of the heartworm life cycle, which in turn allows one to understand treatment and prevention strategies.

As a note, the majority of the information referenced in these proceedings can be located at http://www.heartwormsociety.org.

The life cycle
Before we get to the nuts and bolts of the life cycle, there are a few important points:

1) Many animals can become infected with heartworm, including humans. While the heartworms may not develop to patent adults in many species, they can develop "part of the way." Domestic and wild canids are considered to be the definitive hosts.

2) There is no age-related immunity against heartworm. Any age animal can become infected, and previous infection does not impart immunity to future infections.

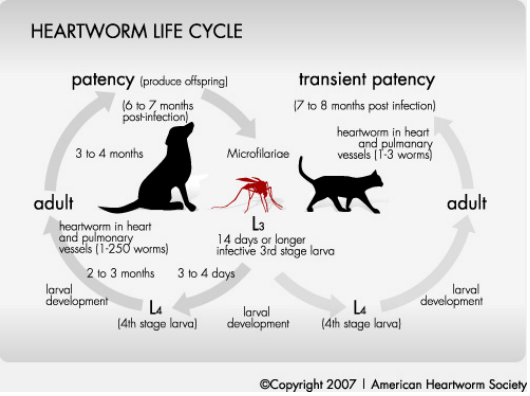
Also, before we delve into the details of the life cycle there are a few questions for one to consider:

True or False…

1. If you take microfilariae from one dog and put those into another dog (e.g. blood transfusion), adult heartworms will develop in that dog.

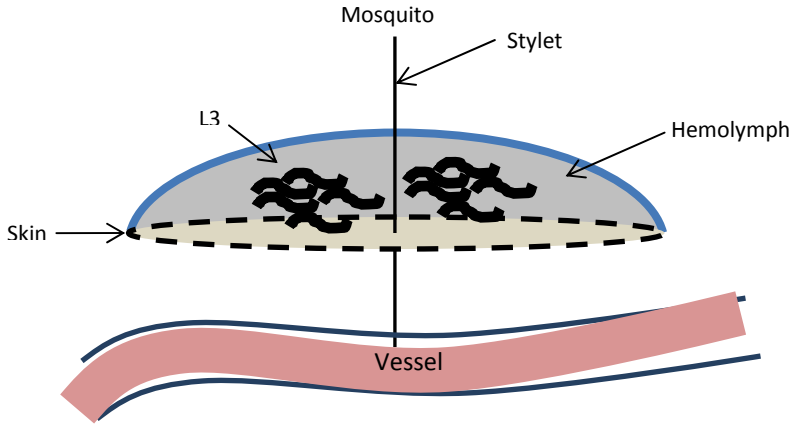
2. You should treat a 7-week old puppy that is microfilaremic for adult heartworm.

The life is depicted in graphic below (from the American Heartworm Society)



We will now consider the important stages of *D. immitis* in relation to the life cycle. The most logical place to start is with the adult worms. Female worms can grow to 10 –12 inches, where males can grow to a length of 4 – 6 inches. Adults can live up to 5 to 7 years in dogs. During this time, the adults will mate and produce microfilariae (>300 microns in length), which circulate in the blood. The microfilariae can then be ingested by a mosquito

intermediate host. The mosquito is ABSOLUTELY REQUIRED for heartworm to develop. Once inside the mosquito, the microfilaria migrate within the mosquito for an average period of approximately 14 days, during which time, the microfilaria develops to a first-stage larvae (L1.) Afterwards, the L1 molts twice to become an infectious third-stage larva (L3), which at this point is in the head of the mosquito. The L3 is approximately one mm in length. Upon landing on a host, the mosquito will then take a bloodmeal. At this point, the mosquito will "bust out" of the proboscis, which is essentially the mouthparts. The larvae will then "surround" the stylet (the piercing part of the mouthparts) in a pool of mosquito hemolymph, as shown in the schematic below:



When the stylet is removed, the larvae then enter the host through the hole made by the stylet. This is in contrast to the commonly-held belief that the larvae are "injected" into the host.

Once inside the definitive host, the L3s follow a complicated migration pathway. The L3 remains at the sight of entrance for approximately 3-4 days. Also during this time, L3 molt to fourth-stage larvae (L4). This is normally completed by 4 days, but may not occur until day 12 post-infection. It is generally agreed that the molt to the last stage, known as the juvenile adult occurs by day 58. By day 70 is when worms first arrive in their final location, the pulmonary artery. Most worms have reached this location by day 120. By day 180, worms are sexually mature and have begun to produce microfilariae, thus completing the life cycle. It is important to realize that while this is the generally accepted life cycle, there could be variations in these times.

The vector as part of the life cycle

A whole lecture could be given on the mosquito vector and its role in transmission of heartworm. Currently over 70 species of mosquitoes are thought to be potential vectors of heartworm, although 10 to 12 species are thought to be most important. While these are the documented species, it is important to remember that there could be yet unidentified species, or newly introduced species, such as the Asian Tiger mosquito, which could also serve as vectors.

An important concept in relation to the role of the mosquito is the concept of seasonal transmisson of heartworm. Maturation of parasites in mosquitoes requires higher temperatures. Practically what this means is that in most of US, the peak months of transmission are July & August. In the Northern US the transmission season is approximately 4 months, whereas in the southern US the transmission season is approximately 6-8 months. There is some speculation that "heat islands" in urban areas could extend the transmission season. In further southern climates, the transmission season would be extended even longer. In the Western United States, there is evidence of transmission, but at a much lower rate than the Southeast United States, where heartworm is endemic. However, with the current recommendation by the American Heartworm Society of administration of year-round heartworm prevention, tailoring prevention strategies for a specific locale has become moot.

Pathology of Heartworm Disease
Heartworm can be a deadly disease, especially when there are a large number of worms (caval syndrome.) While this acute presentation is spectacular, more often than not, we observe pathology secondary to the prolonged presence of worms. The severity of disease and extent of pathology can be the result of a myriad of factors, such as:

1. numbers of adult worms
2. duration of infection
3. individual host immune response
4. presence of dead worms

This last point is especially important as dead worms can "break up" and cause pulmonary thromboembolism, secondary to dying worms. One must remember that the heartworms are literally thrashing in the vessels multiple times a minute, like a bullwhip cracking the paint off of a wall. The trauma to the vessels results in thickening of the tunica intima and inflammation of the vessel wall, characterized by the pathognomonic roughened, stippled appearance. This prolonged damage can eventually lead to vessel inelasticity, which increases pressure on the main pulmonary artery, right heart and vena cava. This leads to chronic, passive congestion and pulmonary hypertension, resulting in right heart enlargement and eventually failure. The right-sided heart failure then leads to liver disease and ascites. Also, renal lesions, such as glomerulomephritis, can develop secondary to immune-mediated disease.

Wolbachia
While the worms themselves can cause damage, more recent data suggests that in fact it is bacteria that causes much of the inflammation associated with heartworm disease. By now, most people have heard of Wolbachia, which an endosymbiotic bacteria of many filarial worms. It seems to be transmitted vertically, and when in living a worm does not cause any overt pathology. The issue is when the worms die either of natural causes or due to drug treatment. When the surface proteins of Wolbachia are exposed to the host, the host immune system responds quite strongly. Because of the damage Wolbachia can do, it is important to eliminate it from the worms prior to treatment.

Clinical signs
Dogs infected with heartworm may present with severe clinical signs, be asymptomatic, or be somewhere in the middle of the spectrum. The severity of clinical signs, like the pathology of heartworm disease, is dependent of many factors. Ultimately, the presence or absence of clinical signs is an important component of staging heartworm disease. These are described briefly below. While these "classes" are presented as absolutes, it must be emphasized that there is a continuum. Full details are available at www.heartwormsociety.org.

With Class I heartworm disease, the animal can be asymptomatic or present with a mild cough. Otherwise, these animals are fine, and do not seem inhibited by the disease.

Animals with Class II heartworm disease will have a more moderate cough. Also, these animals could have difficulty breathing, and be somewhat exercise intolerant.

To be blunt, Class III is when things are going to "hell in a handbasket," so to speak. These animals are dyspneic, and can be severely exercise intolerant. Syncope and hemoptysis may be present. Signs of right-sided congestive heart failure, such as ascites, could be present.

'Caval Syndrome'
The first three classes of heartworm disease apply to signs associated with chronic heartworm disease. Class IV heartworm disease is associated with acute presentation of signs, normally associated with the presence of a large

numbers of worms obstructing blood flow through the tricuspid valve. Hemoglobinemia and pigmenturia are components of this syndrome. The onset is rapid and if not treated will result in death in 12-72 hours.

Animals presenting with caval syndrome are poor candidates for treatment by the traditional method. The treatment of choice is surgical removal. If possible, these animals should be referred to a specialist. If cost is an issue, which is very likely, you can perform the surgery yourself. Regardless of whether or these animals are referred, they will die without surgical intervention.

Diagnosis
Briefly, the method of choice is the antigen test, which tests for the presence of the heartworm female uterine antigen in the blood. This antigen can be detected as early as five months post-infection. There are a variety of tests on the market. Some recent tests claim to also detect antigen from male worms.

Prevention
Heartworm preventives, as a rule, are given monthly to kill the migrating stages of heartworm acquired during the previous month. They do not kill "forward." That is, the drugs do not work by killing infective L3s acquired after administration of the preventive. Most of these preventives, which are of the macrocyclic lactone drug class, either by themselves or when combined with another compound, are effective against certain intestinal parasites or flea life stages. One obvious exception to this is ProHeart 6, which is an injectable preventive that protects for six months.

Treatment
Immiticide is both the treatment of choice, and the only drug APPROVED for treatment of adult heartworm. The 3-injection protocol is recommended by the American Heartworm Society. This treatment will be detailed extensively in another lecture.

Heartworm treatment: making sense of it all
When Immiticide (melarsomine dihydrochloride) first came on the market in the mid-1990's, it was an immense improvement over the days of Carposolate. Caparsolate was injected intravenously, and while effective could have particularly nasty side effects, including skin sloughing. Early treatment protocols for Immiticide involved a 2-dose injection protocol that was quite straightforward. With advances in knowledge about heartworm, the treatment protocol for heartworm has become more complicated. In this lecture, we will cover the staging and treatment of heartworm in the context of these newer and continually evolving recommendations.

As a note, the majority of the information referenced in these proceedings can be located at www.heartwormsociety.org.

Diagnosis of heartworm
Obviously, one must diagnose heartworm before treating. While Immiticide is a safe drug, complications can result, and therefore no one should ever treat heartworm empirically. These diagnostics are absolutely essential to determining the class of heartworm disease. By determining the stage of heartworm disease, you will know whether the animal has improved after treatment, and more importantly, how much at risk the animal is for complications. The higher the class, the greater the risk. The classes are summarized below:

<u>Class I (Mild)</u>
These animals are normally asymptomatic or can have a mild cough. Otherwise, these animals are fine, and do not seem to be inhibited by the disease.

<u>Class II (Moderate)</u>
These animals will have a more moderate cough. Also, these animals could have difficulty breathing, and be somewhat exercise intolerant.

Class III (Severe)
These animals are dyspneic, and can be severely exercise intolerant. Syncope and hemoptysis may be present. Signs of right-sided congestive heart failure, such as ascites, will definitely be present.

Class IV (Caval Syndrome, life-threatening)
Class IV heartworm disease is associated with acute presentation of signs, normally associated with the presence of a large numbers of worms obstructing blood flow through tricuspid valve. Hemoglobinemia and pigmenturia are components of this syndrome. The onset is rapid and if not treated will result in death in 12-72 hours.

Tests and Procedures
The following is a list of tests and procedures for heartworm with a brief description of each:

1. History, physical exam: A history of exercise tolerance, and presentation with dyspnea or signs of congestive heart failure can be indicative of heartworm disease. Crackling or moist rales, and/or a split second heart sound may also be present.

2. Immunodiagnosis: The antigen test is considered the "gold standard" for heartworm diagnosis. There are many types available for in-clinic use. There are too many to cover everyone in detail.

There are some basics concerning antigen tests. As a rule, the tests are highly sensitive and specific for infections with adult female worms > 8 months of age, since older worms tend to produce more antigen. However, single sex infections of only males will not be detected. Also, it is extremely important to remember that tests DO NOT detect prepatent infections (< 5 mo. worms). A summary of the factors affecting the sensitivity of antigen tests is as follows:

1. Sex - only female worms are detected (by most tests)
2. Age of worms – more important than number in diagnosis
a. < 4 months old -- none detected
b. 5 months old -- some detected
c. 6 months old -- most detected
d. 7 months old -- practically all detected
e. > 8 months -- all are consistently detected
3. Number of worms (> 8 months)
    a. 1 female = 62 - 86%
    b. 2 females = 85 - 95%
    c. > 3 females = 93 - 99%

However, it is important to note that antigen tests are not "quantitative." The "color" of any test cannot be correlated to worm burden. Finally, antigen tests can be used to determine effectiveness of adulticidal treatment. If all the worms are killed, adult antigen should be cleared from the blood by 3 months after treatment.

3. Test for microfilaria (mf): Examination of the blood for mf was the definitive way to diagnose heartworm before the advent of the antigen test. Some practices still examine the blood for mf as the primary diagnostic method for heartworm. This is not a best practice, however.
When examining a drop of blood or "direct smear," one will only detect ~75% of patent infections. The ideal means to detect mf is to use a concentration technique, such as the Knott test or a filter test. One of these tests should be used after a positive antigen test, in order to determine the relative amount of mf.

Also, it is important to differentiate *D. immitis* from *Acanthocheilonema (Dipetalonema) reconditum*. This nonpathogenic worm lives in the subcutaneous tissue and is transmitted by fleas. Its mf are also in blood. The

major concern is that one would not want to treat an *A. reconditum*-positive dog for heartworm. This has become must less of a problem with the advent of antigen tests.

4. Radiography: This is an important part of staging the disease, as it allows one to assess the damage that has already occurred. Radiographic findings of heartworm will not be covered extensively in this lecture.

5. Echocardiography: Echocardiography is not a typical diagnostic method for heartworm. However, if one can visualize the heartworms via echocardiography, you may be able to infer their exact location and number.

6. CBC, Chemistry panel and Urinalysis: Liver and kidney function need to be assessed before administration of Immiticide. One needs to know what existing disease is present prior to treatment. Furthermore, the presence of heartworms in the vessels can cause hemolysis.

Treatment Considerations

Before we discuss the actual treatment regimen, it should be stated that pulmonary thromboembolism (PTE) and pulmonary damage are inevitable consequences of successful adulticide therapy. While no known tests are predictive for PTE, the severity can frequently be anticipated based on the stage of disease. Also, the more worms that are present, the more likely the risk of PTE.

The clinical signs of embolism include fever, cough, hemoptysis, and exacerbation of right heart failure. These are usually evident within 7-10 days, but may occur for up to 4 weeks post-treatment. For this reason, exercise restriction for four weeks post-treatment is essential. This part of treatment can be the most difficult to implement, but cage-rest (leash walk only) is as an important part of the regimen as the Immiticide injections.

The treatment protocol

The full treatment guidelines are available at http://www.heartwormsociety.org. What follows highlights some important components of heartworm treatment.

1. Melarsomine dihydrochloride (Immiticide)

The standard 2-dose regimen for Immiticide is 2 intramuscular injections give in the epaxial muscles, each at 2.5 mg/kg. This is still the labeled protocol; however, the alternate or 3-dose regimen is what is recommended by the American Heartworm Society. For the 3-dose protocol, 1 injection at 2.5 mg/kg is given, and then 1 month later, 2 more doses are administered 24 hr apart. The advantage of the 3-dose regimen is increased safety and efficacy. The obvious disadvantages are an additional month of exercise restriction, an increase in the total arsenical dose, and the additional cost of a third injection.

2. Macrocyclic lactones (ML)

It is now recommended that one should start a ML preventive (mainly ivermectin, which has been used in most studies) at the time of diagnosis, or up to 3 months prior to Immiticide treatment. The advantage of this is that further infection is prevented and developing larvae are damaged or eliminated. Furthermore, the administration of a ML, while delaying treatment also eliminates the "treatment/susceptibility" gap. By reducing the treatment gap, you eliminate worms <2 months of age, and allow maturation of 2-4 month old worms to the point to where they can be killed using Immiticide.

There is also evidence that ivermectin may reduce mass and health of existing heartworms. By reducing the mass of worms before killing them, you should be reducing the risk of PTE.

3. Steroids

Prednisone can be used. The dosage recommendations have been a bit "fluid." For the latest information, I would refer to the American Heartworm Society treatment guidelines.

4. Doxycycline

This antibiotic has become a very important drug in the treatment of heartworm, due to its activity against the bacterial endosymbiont, Wolbachia. There are some differing opinions as to when to administer it prior to adulticide treatment. What is agreed upon is the dose- 10 mg/kg BID PO, and the duration of administration- 4 weeks. Some people administer doxycycline the month prior to treatment, while others administer it immediately upon diagnosis (i.e. the first month of the 2 to 3 month treatment gap).

At the writing of these proceedings, doxycycline is in variable supply. Alternatives are being investigated.

Conclusion

Heartworm treatment recommendations are constantly changing. It is important to keep current on information, with the best source being the American Heartworm Society.

Heartworm preventives: a brave new world

Heartworm infection can be life threatening. As with many parasites, an ounce of prevention is worth a pound of cure. Due to the pathologic changes that occur due to heartworm infection, as well as the associated cost of treatment, prevention of heartworm is a necessity, not a luxury. Convincing clients of this necessity in the age of the internet, coupled with recent reports of lack of efficacy, has created challenges that were not present ten years ago. It truly has become a brave new world.

As a note, the majority of the information referenced in these proceedings can be located at http://www.heartwormsociety.org.

The life cycle:

Before we can discuss the challenges associated with heartworm prevention, we must first discuss how preventives function in relation to the life cycle.

The most logical place to start is with the adult worms, which live in the pulmonary arteries and heart. Adults can live up to 5-7 years in dogs. During this time, adults will mate and produce microfilariae, which circulate in the blood. The microfilariae are then ingested by a mosquito intermediate host. The mosquito is ABSOLUTELY REQUIRED for the heartworm to develop. Once inside the mosquito, the microfilaria migrate within the mosquito for an average period of approximately 14 days, during which time, the microfilariae develop to a first-stage larvae. After this, they molt twice to become an infectious third-stage larvae (L3), which at this point is in the head of the mosquito. The L3s are approximately one mm in length. Upon landing on a host, the mosquito will then take a bloodmeal. During feeding, the larvae will "bust out" of the proboscis. When the mosquito removes its stylet, the larvae then enters the host through the hole made by the stylet. This is in contrast to the commonly-held belief that the larvae are "injected" into the host.

Once inside the definitive host, the L3s follow a complicated migration pathway. The L3 remains in the vicinity of the sight of entrance for approximately 3-4 days. Also during this time, L3 undergoes a molt to the fourth-stage larvae (L4). This is normally completed by 4 days post-infection, but could not occur until day 12 post-infection. This is the most important part of the life cycle with regards to prevention. Heartworm preventives, as a rule, kill the migrating stages of heartworm acquired during the previous month. They do not kill "forward." That is, the drugs do not work by killing infective L3s acquired after administration of the preventive.

It is generally agreed that the molt to the last stage, known as the juvenile adult, occurs by day 58. At day 70, the worms first arrive at their final location, the pulmonary artery. Most worms have reached this location by day 120. By day 180, worms are sexually mature and have begun to produce microfilariae, thus completing the life cycle. It is important to realize that while this is the generally accepted life cycle, there could be variations in these times.

A brief history of the evolution of heartworm preventives:
(Disclaimer: Mention or lack thereof of a particular product does not constitute bias on the author's part. At this point, it is almost impossible to mention every domestic small animal parasiticide on the market. Also, company names are mentioned as they are currently, not when the product was developed.)

Initially, heartworm preventives were administered daily and contained diethylcarbamazine (DEC). The most well-known of these was Filaribits®, which many of us still remember (although, there are more and more blank stares when I mention this drug to veterinary students). In the mid-1980's, preventives underwent a monumental change that has shifted the industry forever. This is when the first ivermectin-based monthly preventive was launched. A monthly preventive can kill migrating third and early fourth-stage larvae, thus giving it a distinct advantage over a daily dose of DEC, which is effective at a distinct point in the life cycle. With monthly prevention, owners had less "pills" to remember, and veterinarians no longer had to stock boxes and boxes of bottles containing daily preventives in their practice bathrooms and offices. The industry has not looked back, since the advent of the monthly preventive.

Ivermectin is in the macrocyclic lactone class of drugs. Macrocyclic lactone drugs contain all currently labeled heartworm preventives. These drugs are administered monthly with one exception discussed below. Ivermectin is normally combined with pyrantel. This combination of ivermectin and pyrantel was the start of another important shift in the industry: the combination product. Now with ivermectin and pyrantel, one could "prevent" heartworm, as well as treat and control certain intestinal parasites, specifically hookworm and roundworm.

Next on the market was milbemycin oxime. Milbemycin oxime had an advantage over the ivermectin/pyrantel-based drugs in that it was also labeled for whipworms. Milbemycin oxime would later be combined with the flea preventive lufenuron.

Next to market was selamectin in a topical formulation, which was unique at the time because it was a topical versus oral heartworm preventive. While anecdotally, most clients prefer to give their dog a pill, some do prefer administering drugs topically. Also, a topical formulation provided cat owners a much easier route to administer a heartworm/intestinal preventive to their pet.

Another topical, containing moxidectin would come to market, thereafter. Topical moxidectin was combined with the flea preventive, imidacloprid. This formulation like milbemycin will treat and control whipworm.

Finally, quite a few years ago, a combination of milbemycin oxime and spinosid, a flea adulticide, hit the market.

But wait, you forgot one…
The 6-month injectable moxidectin formulation is back on the market, and is deemed safe by the FDA. This formulation offers the non-compliant client a means to protect their pet from heartworm for 6 months. It also requires very little inventory space on your shelf when compared to its monthly competitors.

A brave new world…
There are many perceived problems surrounding monthly parasite prevention. I cannot begin to detail every one. However, I have listed the most important and pressing issues.

1. Internet Pharmacies: This debate could and has dominated hour-long roundtable discussions. As cost has become more of an issue in the eyes of the client, they have turned to these "cheaper" sources. Another problem, product diversion, allows these pharmacies to thrive. The "grey" market, which buys products from veterinarians, and then sells them to these pharmacies, is the central culprit.

2. "I read on the internet…": Clients increasingly turn to the internet in order to obtain veterinary advice. While some sites are reputable, many are not. Unfortunately, clients cannot always tell the difference. This could lead to use of internet pharmacies and unproven herbal remedies.

3. Cost: With more limited income, clients have to make tough choices between preventives and other necessities.

4. Lack of efficacy cases: Reports of suspected lack of efficacies, which cannot be attributed to non-compliance or a failure to administer preventives correctly, has raised doubts among both clients and veterinarians about these products.

5. Not communicating the value of prevention to the client: As veterinarians, we need to send a consistent message of compliance starting with the front desk, then the technician, and finally the veterinarian. We need to emphasize not only the importance of prevention, but the importance of the veterinarian's role in tailoring a parasite prevention program to the individual client. The internet will never be able to accomplish this task.

While there are many new challenges ahead of the profession with regards to parasite prevention, I believe that we can address these issues by emphasizing the value of these products to the client, and more importantly their pet.