Summary of the Current Feline Guidelines for the

Prevention, Diagnosis, and Management of Heartworm *(Dirofilaria immitis)* Infection in Cats[1]

Prepared for and approved by the Executive Board of the American Heartworm Society[2]

AMERICAN HEARTWORM SOCIETY
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EPIDEMIOLOGY

Heartworm infection has been diagnosed around the globe, including all 50 of the United States, and is considered at least regionally endemic in each of the contiguous 48 states and Hawaii. The relocation of microfilaremic dogs and expansion of the territories of microfilaremic wild canids in other areas of the US continue to be important factors contributing to further dissemination of the parasite. Environmental changes created by humans, such as the formation of "heat islands" due to urban sprawl, and changes in natural climatic conditions have increased heartworm infection potential by creating microenvironments that support development of heartworm larvae in mosquito vectors during colder months, thereby lengthening the transmission season.

BIOLOGY OF FELINE HEARTWORM INFECTION

Significant differences exist between feline heartworm disease and its classical canine counterpart. Although cats are susceptible hosts, they are more resistant to infection with adult *Dirofilaria immitis* than are dogs. Most heartworm infections in cats are comparatively light and consist of less than six adult worms. Typically only one or two worms are present and worms in approximately one third of infections are single sex. Cats with only a few worms are still considered to be heavily infected in terms of parasite biomass, however, because of their relatively small body size.

Host preference by some of the most abundant vectors does favor the dog and may contribute to the lower prevalence of infection in cats. The *Culex* spp mosquito, which is the most common species in many urban areas, feeds on both cats and dogs without preference. The true prevalence of heartworm infection in cats is probably understated due to diagnostic limitations and the greater tendency of cats to exhibit only transient clinical signs or die without confirmation of infection. Necropsy surveys of shelter cats have placed the prevalence of adult heartworm infections at 5% to 15% of the rate in unprotected dogs in a given area. Circulating microfilariae are seldom found in infected cats. When microfilaremia does develop in cats, they appear only about one week later than in dogs (195 days post infection at the earliest), and seldom persist beyond 228 days post infection. Heartworms transplanted

[1] These recommendations, revised in January 2014, supersede previous editions and are based on the latest information presented at the 2013 Triennial Symposium of the American Heartworm Society (AHS), new research, and additional clinical experience, and have been peer reviewed by independent experts. The complete version of the 2014 Feline Guidelines can be found at the American Heartworm Society's website, www.heartwormsociety.org.

[2] Officers: Dr. Stephen Jones, President; Dr. Wallace Graham, Past President; Dr. Cristiano von Simson, Vice President; Dr. Robert Stannard, Secretary-Treasurer; Dr. Doug Carithers, Editor; Dr. Patricia Payne, Dr. Chris Rehm, Dr. Charles Thomas Nelson, Dr. Martha Smith-Blackmore, Dr. Elizabeth Clyde and, Dr. Bianca Zaffarano Board Members; Dr. Matthew Miller, Symposium Chair; Dr. Clarke Atkins, Symposium Co-Chair; Dr. John McCall, Co-Editor; Dr. Mike Loenser and Dr. Tony Rumschlag, Ex Officio Members.

from cats are capable of resuming production of circulating microfilariae in dogs; thus, it appears feline infections become occult due to host immune-mediated clearance of the microfilariae and perhaps a reversible suppression of microfilariae production. There are other indications that the cat is an imperfect host for heartworms. Aberrant migration occurs more frequently in cats than in dogs. Although uncommon, heartworms are found disproportionately often in the body cavities, systemic arteries, and central nervous system of cats. In addition, the life span of the parasite in cats is thought to be 2 to 3 years or even longer, which is considerably shorter than that in dogs. Nevertheless, heartworms are capable of causing severe disease in cats.

PATHOPHYSIOLOGY

The clinical importance of heartworms is amplified in cats because even a small number of heartworms are potentially life threatening. Although live adult worms in the pulmonary arteries cause a local arteritis, some cats never manifest clinical signs. When signs are evident, they usually develop during two stages of the disease: 1) arrival of heartworms in the pulmonary vasculature and 2) death of adult heartworms. The first stage occurs approximately 3 to 4 months post infection with an acute vascular and parenchymal inflammatory response to the newly arriving worms and the subsequent death of most of these same worms. This initial phase is often misdiagnosed as asthma or allergic bronchitis but in actuality is part of a syndrome known as *heartworm-associated respiratory disease* (HARD). Clinical signs associated with this acute phase subside as the worms mature but demonstrable histopathologic lesions, most notably occlusive medial hypertrophy of the small pulmonary arterioles, are evident even in those cats that clear the infection. Once the pulmonary infection is established, evidence suggests that live heartworms are able to suppress immune function. This allows many cats to tolerate their infection without apparent ill effects—that is, until the mature worms begin to die, which initiates the second stage of disease expression. The degenerating parasites can cause pulmonary inflammation and thromboembolism, which often leads to fatal acute lung injury. Such reactions in cats can occur even in single-worm infections.

Caval syndrome occurs rarely in cats compared with dogs as infections are usually light, but even one or two worms can cause tricuspid regurgitation and resultant heart murmur. Arterial intimal proliferation resembling the characteristic heartworm arteritis found in dogs also develops in the major lobar and peripheral pulmonary arteries of cats but usually fails to cause sufficient obstruction to produce clinically significant pulmonary hypertension.

PHYSICAL DIAGNOSIS

Many cats tolerate their infection without any noticeable clinical signs or with signs manifested only transiently. Clinical signs associated with feline heartworm disease may be only a vague malaise or can comprise predominantly respiratory, gastrointestinal (e.g., emesis), or occasionally neurologic manifestations, chronically or acutely. Signs of chronic respiratory disease, such as persistent tachypnea, intermittent coughing, and increased respiratory, effort are most common. A systolic heart murmur may be present in cats when worms reside in the right atrioventricular junction interfering with tricuspid valvular function. Anorexia and weight loss occur in some cats. Intermittent vomiting unrelated to eating is reported frequently, and in endemic areas when no other cause is evident should raise suspicion of heartworm infection. A peracute syndrome of signs including respiratory distress, ataxia, collapse, seizures, hemoptysis, or sometimes sudden death may occur.

DIAGNOSTIC TESTING

Heartworm infection in cats is a more elusive diagnosis than in dogs and can be easily overlooked. A conscious awareness of its existence is critical. Establishing a definitive antemortem diagnosis frequently entails application of multiple diagnostic tests, some of which may need to be repeated. Of these, heartworm serology, thoracic radiography, and echocardiography are the most useful methods of clinical confirmation.

Microfilariae. Cats are seldom microfilaremic when examined. Since few microfilariae are ever present, the chances of finding them are improved by using concentration techniques (modified Knott or millipore filter).

Serology. Interpretation of antibody and antigen test results is complicated and a thorough understanding of the limitations of both tests is necessary in order to use these assays with confidence. In dogs, the **antigen test** is the "gold standard" but because infections consisting of only male worms or symptomatic immature infections are more common in cats, none of the presently available antigen tests

can be relied upon to rule out heartworm disease in cats. The current generation of heartworm antigen tests identify most "occult" infections (adult worms present but no circulating microfilariae) consisting of at least one mature female worm and are nearly 100% specific. Necropsy surveys of shelter cats have shown that 50% to 70% of infected cats have at least one female worm. Detectable antigenemia develops at about 5.5 to 8 months post infection. False-negative test results occur most commonly when infections are light, female worms are still immature, only male worms are present, and/or the test kit instructions have not been followed. There are also documented cases of antigen-antibody complexes interfering with antigen testing resulting in false-negative tests. Heating the sample test-tube in a warm water bath to 104°C for 10 minutes will break these complexes down, releasing any antigen, resulting in more accurate test results. Heartworm test results should only be recorded as positive or no antigen detected (NAD) and should not be written as "negative."

Antibody tests have the advantage of being able to detect infection by both male and female worms, as larvae of either sex can stimulate a detectable immune response as early as 2 months post infection. Antibody tests do not offer an indication of the continued existence of an infection, however, just that an infection occurred. Initial research reported the sensitivity and specificity of the feline antibody tests to be as high as 98% in cats experimentally infected with adult worms. Necropsy surveys of naturally infected cats from shelters, however, have indicated a lower sensitivity ranging from 32% to 89%. The different antibody tests vary in their sensitivity to each stage of larval development; thus, discordant results between test methods are common. Limited evidence from several studies suggests that the antibody level in cats decreases with time as the parasite matures and that heartworm-infected cats with clinical signs are more likely to be antibody positive than infected asymptomatic cats. Correct interpretation of antibody tests results requires additional information and thoughtful analysis.

Since both juvenile and adult worms are capable of causing clinical disease in the cat, both antibody and antigen tests are useful tools and when used together increase the probability of making appropriate diagnostic decisions.

Thoracic Radiography. Thoracic radiography may provide strong supportive evidence of feline heartworm disease. It is valuable for assessing the severity of disease and monitoring its progression or regression as well as eliminating other differential diagnoses. The most characteristic radiographic features of heartworm disease in cats, as in dogs, are a sometimes subtle enlargement of the main lobar and peripheral pulmonary arteries, characterized by loss of taper, and sometimes tortuosity and truncation in the caudal lobar branches. These vascular features are visualized best in the ventrodorsal view and are sometimes visible only in the right caudal lobar artery, where heartworms are found most often. Enlargement of the main pulmonary artery segment may occur in heavily infected cats but is not a reliable marker, since most cats do not develop pulmonary hypertension and because the main pulmonary artery is obscured by the cardiac silhouette. The cardiac silhouette itself is seldom enlarged. A bronchointerstitial lung pattern that may clear spontaneously within a few months is a common secondary feature suggestive of but not unique to feline heartworm disease. In some cases, thoracic radiographs provide no evidence of infection. Radiographic features suggestive of heartworm disease can be found in about half of the cats suspected of being infected based on historical and physical signs. In addition, about half of those cats with pulmonary arterial enlargement indicative of heartworm disease are antibody positive. Temporal differences in the development of the parasite, host immune responses, and spontaneous regression of lesions may account for discrepancies between radiographic, clinical, and serologic findings. Infection with *Toxocara cati and Aelurostongylus* spp can cause similar radiographic patterns and must be considered in a differential diagnosis.

Echocardiography. The chambers of the right side of the feline heart can be thoroughly interrogated by two-dimensional echocardiography. Images of the main pulmonary artery and a long segment of the proximal right and a very short portion of the left pulmonary arteries can also be obtained. Although heartworms are found most often in the main and right lobar branch of the pulmonary artery, it is necessary to methodically interrogate all of these locations because worms in a typical light infection may occupy only one site. An adult heartworm is relatively long compared with the length of the pulmonary arteries in cats. Therefore, there is a better chance in cats than in dogs of finding heartworms extending from peripheral branches into

proximal segments where they can be visualized. An experienced sonographer has a very good chance of making a definitive diagnosis in cats that are actually infected with adult heartworms, particularly when there are several worms. In suspected cases, the high specificity of this examination generally allows for confirmation of heartworm infection of at least 5 months' duration. Quantification of worm burden is difficult.

Necropsy Confirmation. A complete necropsy should be performed in any cat suspected of dying of heartworm disease or in which the cause of sudden death is unexplained. A thorough search of the vena cavae, right side of the heart, and pulmonary arteries must be performed because one or two worms easily can be overlooked, particularly if immature, dead, and fragmented. Special attention should be paid to examining the most distal aspects of the pulmonary arteries as dead worms would be forced and compressed to this position by blood flow. Heartworms occasionally are restricted to ectopic sites, so the systemic arteries, body cavities and, if neurologic signs were present, the brain and spinal canal should also be examined thoroughly.

TREATMENT

Medical Options. If a cat displays no overt clinical signs despite radiographic evidence of pulmonary vascular/interstitial lung disease consistent with heartworm disease, it may be prudent to allow time for a spontaneous cure to occur. The course of infection can be monitored at 6- to 12-month intervals by repeat antibody and antigen testing and thoracic radiography. In those cats destined to recover, regression of radiographic signs and especially seroconversion of a positive antigen test to negative status provide evidence that the period of risk probably has passed.

Prednisone in diminishing doses often is effective medical support for infected cats with radiographic evidence of lung disease whether or not they appear ill. Prednisone also should be initiated whenever antibody- and/or antigen-positive cats display clinical signs. An empirical oral regimen is 2 mg/kg body weight/day, declining gradually to 0.5 mg/kg every other day by 2 weeks and then discontinued after an additional 2 weeks. At that time the effects of treatment should be reassessed based on the clinical response and/or thoracic radiography. This treatment may be repeated in cats with recurrent clinical signs.

Cats that become acutely ill need to be stabilized promptly with supportive therapy appropriate for treating shock; this may include intravenous corticosteroids, balanced electrolyte solutions, bronchodilators, and oxygen via intranasal catheter or closed cage. Diuretics are inappropriate, even for infected cats with severe interstitial or patchy alveolar lung patterns. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have failed to produce demonstrable benefit.

Adulticide (melarsomine dihydrochloride) use is not recommended for use in cats due to insufficient experience and preliminary data which suggest that melarsomine is toxic to cats at doses as low as 3.5 mg/kg. Ivermectin administered at 24 µg/kg monthly given for 2 years has been reported to reduce worm burdens by 65% as compared with untreated cats. Because most cats have small worm burdens, it is not worm mass alone that is problematic but the "anaphylactic" type reaction that results when the worms die. To date, there are no studies that indicate any form of medical adulticidal therapy increases the survival rate of cats harboring adult heartworms.

Surgical Options. In principle, it is preferable to remove heartworms rather than destroy them *in situ*. This can be accomplished successfully by introducing brush strings, basket catheters, or loop snares via right jugular venotomy or, alternatively, after left thoracotomy, alligator forceps can be inserted through a right ventricular purse-string incision. Heartworms first should be identified ultrasonographically in locations that can be reached with these inflexible instruments. Although it may not be possible to retrieve every worm, the surgical option may be a reasonable alternative to symptomatic support or adulticide treatment of cats that are heavily infected and/or are in critical condition. Surgery is specifically indicated in those few cases that develop caval syndrome. Care must be taken to remove the worms intact; partial or complete traumatic transection of a worm almost invariably results in acute circulatory collapse and death.

ADDITIONAL CONSIDERATIONS FOR ADULTICIDE THERAPY

Wolbachia. Most filarial nematodes, including *D immitis*, harbor obligate, intracellular, gram-negative bacteria belonging to the genus *Wolbachia (Rickettsiales)*. These bacteria have been implicated in the pathogenesis of filarial diseases, possibly through their endotoxins. Recent studies have shown that a major surface protein of *Wolbachia*

(WSP) induces a specific IgG response in hosts infected by *D immitis*. It is hypothesized that *Wolbachia* contributes to pulmonary and renal inflammation through its surface protein WSP, independently from its endotoxin component. Studies to determine the effects of suppressing *Wolbachia* populations with doxycycline prior to adulticide therapy to determine the clinical utility of this therapeutic approach in cats are in progress.

Surveillance of Infected Cats. Serologic retesting at 6- to 12-month intervals to monitor infection status is recommended for all infected cats whether or not they have clinical signs that are treated empirically or are given medical/surgical adulticide therapy. Once adult heartworm infection has been diagnosed, monitoring will be most informative if both antibody and antigen testing are performed. An annual retest may be adequate for asymptomatic cats. Spontaneous or adulticide-induced elimination of infection in antigen-positive cats ordinarily will be followed within 4 to 5 months by disappearance of detectable antigenemia. Once cats become antigen negative and are clinically normal, further antibody retesting becomes optional because antibody may persist for an indefinite period after the parasites are gone and because continued exposure, even with preventive therapy, will result in a positive test. Radiography and ultrasonography also may be useful for monitoring cats with pulmonary vascular and/or parenchymal lung disease or those in which heartworms have been identified on echocardiography.

CHEMOPROPHYLAXIS

Monthly heartworm preventives are a safe and effective option for cats in areas where heartworm infection is considered endemic in dogs and exposure to infective mosquitoes is possible. So-called "indoor" cats may also be at risk. When monthly heartworm prevention is elected, it should at least be administered for 30 days following the estimated seasonal onset of transmission and continued within 30 to 90 days after that period has ended. Advantages of year-round administration of heartworm preventive include 1) activity against some common intestinal parasites and in the case of selamectin and topical moxidectin + imidacloprid, external parasites, 2) increased compliance, and 3) retroactive efficacy as a safeguard for missed doses. Heartworm prevention can be achieved in cats with monthly doses of either ivermectin or milbemycin oxime orally, or topical moxidectin or selamectin. Preventives should be started in kittens at 8 weeks of age and be administered to all cats in heartworm-endemic areas during the heartworm transmission season. The individual minimum monthly prophylactic dose of ivermectin is 24 µg/kg, milbemycin oxime 2.0 mg/kg, moxidectin 1.0 mg/kg, and selamectin 6 mg/kg body weight. Administration of these drugs in cats is not precluded by antibody or antigen seropositivity.

Seroepidemiologic data for most communities is presently meager; thus, it behooves veterinarians to become familiar with the local risk potential by testing cats before initiating heartworm preventives to establish a serologic benchmark. Although testing cats before starting them on heartworm preventives is recommended, it is less useful than doing so in dogs. This apparent contradiction reflects the differences in testing methods and test performance in the two hosts. Pretesting (screening) dogs is limited to documenting either heartworm antigenemia or circulating microfilariae, both of which are specific indicators of adult worm infection. Many, if not most, cats that are antibody positive have only been transiently infected to the 4th larval stage. Evidence of exposure of a cat to at least 4th stage larvae confirms the potential risk of developing HARD and reinforces justification for recommending preventives. The preferred method for screening includes the use of both an antigen and an antibody test.

Microfilaremia in cats is uncommon, transient, and typically below concentration levels that might trigger an adverse reaction to microfilaricidal preventive drugs; thus pretesting for microfilariae is unnecessary. Furthermore, antibody retesting of cats already committed to prevention provides no assurance of efficacy because sensitization from repetitive aborted precardiac larval infections is possible in cats that are repetitively exposed. Therefore, the primary reasons for heartworm testing cats are 1) to establish an etiologic diagnosis in those individuals that, based on other clinical evidence, are suspected to be infected, 2) to monitor the clinical course of those that have already been diagnosed with feline heartworm disease, and 3) to establish a baseline reference prior to initiating preventives.