ESDA

European Society of Dirofilariosis and Angiostrongylosis

GUIDELINES FOR CLINICAL MANAGEMENT OF FELINE HEARTWORM DISEASE

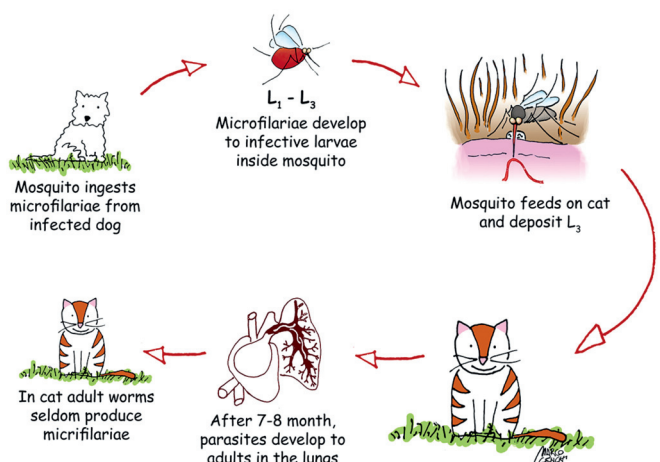## Prepared for and approved by the Executive Board of ESDA

Infection of cats with *Dirofilaria immitis* has been diagnosed in many European countries and is spreading. These guidelines, developed by the European Society for *Dirofilaria* and *Angiostrongylus*, are based on the latest information and include up-to-date recommendations for the prevention, diagnosis, and clinical management of feline heartworm disease (HWD).

Life cycle of *Dirofilaria immitis* in cats

Cats are considered a susceptible, but not ideal, host for *Dirofilaria immitis*. Increased host resistance is reflected by the relatively low adult worm burden in natural infections (cats generally harbour 1 to 6 worms with 2 to 4 worms being the usual burden), the low number of heartworms that develop after experimental inoculation with infective larvae, the prolonged pre-patent period (8 months), the low level (< 10/ml of blood) and short duration (approximately 7 months)of microfilaremia (in only 20% of cats with mature male and female heartworms), and the short life span of adult worms (2-4 years). Finally, adult worms in cats are shorter than those in dogs.

European prevalence

The prevalence of feline heartworm infection is not well known because ante-mortem diagnosis is difficult. It is generally considered to be 5% to 20% that of the infected canine population in the same area. Cats are likely less attractive to mosquito vectors, but *Culex* spp. and *Aedes albopictus*, among the most common mosquitoes,

Mosquito ingests microfilariae from infected dog

$L_1 - L_3$
Microfilariae develop to infective larvae inside mosquito

Mosquito feeds on cat and deposit L_3

In cat adult worms seldom produce micrifilariae

After 7-8 month, parasites develop to adults in the lungs

feed regularly on cats. Given the epidemiology and pathophysiology of the disease, every cat living in are where the infection is present in dogs should be considered at risk. For canine prevalence rates in Europe, please see the ESDA Guideline for canine heartworm disease (www.esda.vet)

Clinical presentation of Feline Heartworm Disease (HWD)

The clinical signs of *D. immitis* infection in cats are very different compared to dogs. Most cats seem to support the infection well for long periods of time. These cats may have spontaneous self-cure due to the natural death of parasites without any clinical manifestations or may suddenly show dramatic, acute symptoms, including sudden death.

When present, the most common clinical signs observed in cats are cough and dyspnoea, sometimes associated with vomiting, unrelated to food intake. Rarely, cats will present with vomiting alone. Chronic coughing, vomiting, diarrhoea, weight loss can also be observed. Contrary to that seen in dogs, symptoms associated with right ventricular heart failure are not considered consistent with heartworm infection in cats. Even though changes in the pulmonary arteries and lungs seem to be similar in cats and dogs, the feline right cardiac chambers support pulmonary hypertension well and right cardiac heart failure is an unusual finding.

Sudden death in apparently healthy cats is a further, typical event.

The pathogenesis of *D. immitis* infection in cats has been the subject of intense study in recent years. The onset of symptoms in most cases seems to be related to the natural death of adult parasites, but it has been more recently hypothesized that the disease develops along several stages. The first phase is associated with the arrival of young, immature worms in the caudal pulmonary arteries approximately 3 months after the infection. The majority of these young parasites die and this causes an acute vascular and parenchymal response, with severe muscular hypertrophy of the medium and small size arteries. Therefore, cats can present pulmonary disease without the presence of fully mature adult worms (see HARD, below).

It is now known that adult worms suppress the activity of pulmonary vascular macrophages, the main component of the feline reticuloendothelial system. Thus, when and if young worms develop to the adult stage, suppression of the immune response, together with resolution of clinical signs, can occur in a second phase of the infection. Once adult worms die (spontaneously or following medical treatment), immune suppression ceases and the most severe forms may appear. Thus, the third phase of disease appears with the degeneration of dead parasites that cause a dramatic inflammatory and thromboembolic response that can lead to sudden or acute death in up to 20% of cats. Finally, in the fourth and final stage, in cats that have survived worm death, hyperplasia of type II alveolar cells replaces the normal type I cells and this may cause permanent respiratory dysfunction and chronic respiratory disease (in absence of worms).

As stated above, cats may experience acute episodes of coughing, dyspnea or intermittent vomiting, known as feline *heartworm-associated respiratory disease* (H.A.R.D.), at around three months post-infection. Since most immature worms do not survive in cats after they reach the caudal pulmonary arteries, it is thought that this acute disease is related to the death and embolization of worms or worm fragments. This induces a strong inflammatory response in the vessels and pulmonary parenchyma with subsequent infarction of the pulmonary parenchyma and circulatory collapse. Other signs of H.A.R.D. may include neurological signs (*e.g.*, ataxia, head tilt, blindness, circling or seizures) and sudden death.

Cats infected with heartworm often self-cure. In a recent study of naturally infected cats with subclinical disease, 28 (82%) self-cured, and 21 of these showed no clinical signs during the study. However, it should be noted that four of the six cats that died during the study showed no overt clinical signs before death.

Aberrant migration, which occurs more frequently in cats than in dogs, is a further indication that the cat is an imperfect host for heartworms. Occasionally, adult worms will migrate to sites other than the heart and the pulmonary arteries, and cause s.c. ectopic infections. Localization of *D. immitis* has been reported in the eye, CNS (cerebral arteries and lateral ventricles), systemic arteries and subcutaneous tissue.

Thoracic Radiographs
(both latero-lateral and dorsoventral views)
Thoracic radiographs are an important tool for the diagnosis of feline heartworm disease. Despite the fact that thoracic abnormalities are often absent or transient, typical findings such as enlargement of the peripheral branches of the pulmonary arteries, accompanied by varying degrees of pulmonary parenchymal disease, are strongly consistent with heartworm infection.

Enlargement of the main pulmonary artery cannot be observed in dorsoventral or ventrodorsal views because this tract of artery is obscured by the cardiac silhouette. Right sided cardiomegaly is not considered a typical finding in the cat.

### B mode, M mode and Doppler Echocardiography
Cardiac ultrasound allows the direct visualization of parasites in the right atrium and ventricle, main pulmonary artery and proximal tract of both its peripheral branches as floating typical double linear parallel hyperechoic structures.

The sensitivity of echocardiography for the detection of heartworm infections in cats is highly operator-dependent and ranges between 88 and 100%. The pulmonary arteries should be evaluated carefully to increase the likelihood of detection of heartworms. Only a short portion of caudal pulmonary arteries, compared with the length of the parasite, cannot be thoroughly examined because of the acoustic impedance of the air-inflated lungs.

Diagnostic specificity is virtually 100%. It is however possible to gain false-positive results when scanning cats at risk for heartworm infection. False positive results are

thought to be caused by the right ventricular chordae tendineae or to the occasional presence of linear echoes that mimic adult heartworms in the main pulmonary artery branches, probably due to reflections from the artery wall. Quantification of worm burden is, nevertheless, difficult because the potential serpentine positioning allows echo beams to transect the worm in multiple sites, giving multiple echo images and potentially over or underestimating worm burden.

Even if most of heartworm-infected cats have histological evidence of pulmonary artery damage, pulmonary hypertension is considered extremely unusual, therefore, echocardiographic signs of right atrial and right ventricular enlargement following pressure overload, as well as the high velocity tricuspid regurgitation on Doppler examination commonly observed in dogs are considered extremely rare in cats.
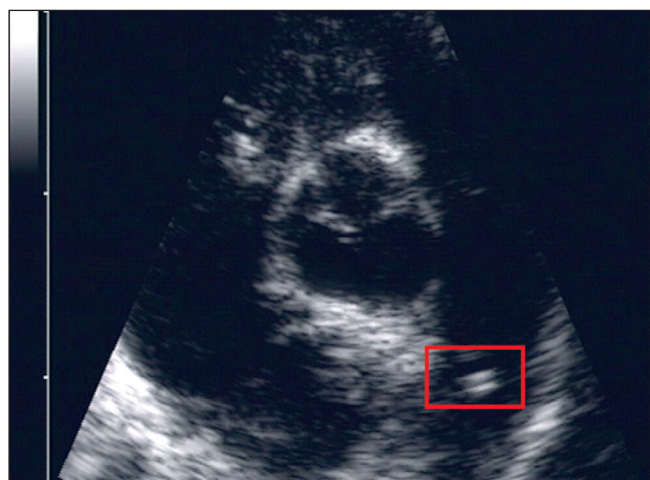
Cross section (typical double linear parallel hyperechoic structures) of an adult Heartworm into the pulmonary artery of a naturally infected cat.

Clinical Pathology

In cats, no significant changes in erythrocytes, platelets and leucocytes concentrations are strictly associated with heartworm infection except for absolute peripheral eosinophilia, which is reported as starting approximately 70 days after infection in experimental conditions. Despite this experimental finding, absolute eosinophilia cannot be considered a good marker of heartworm disease as the percentage of naturally infected cats showing eosinophilia is not known. Moreover, eosinophilia in cats is not a specific alteration but a common finding secondary to several parasitic and allergic diseases.

Diagnosis

Diagnosis of feline heartworm infection is challenging. Due to the differences in the biology of the parasite in the cat, many of the diagnostic methods that are useful, sensitive and specific in the dog are not so in the cat. It is therefore necessary to use a multifaceted approach and to interpret the results of several tests together: thoracic radiography and serum antibody tests to raise the index of suspicion, echocardiography and testing for

both microfilariae and serum antigens to confirm or exclude the presence of adult parasites.

Blood test for microfilariae

Cats are rarely microfilariaemic and sensitivity of detection of is very low. However, when present, specificity is considered 100%, as in dogs.

For information on how to perform a Knott test, go to www.esda.vet

Test for adult heartworm antigens

Tests detecting adult heartworm antigens can provide a definitive proof of infections in cats because of the very high specificity. Unfortunately, worm burden is usually very low in cats, infections caused only by male heartworms are not infrequent and often symptomatology may be due to immature worms. Thus, these tests have a very high specificity for mature infections but sensitivity can be lower in case of low burden or single worm/sex infection. A negative test cannot therefore be considered sufficient to rule out infection. The result should be recorded only as positive or "No Antigen Detected (NAD)", but it should not be considered negative for heartworm infection".

It has been reported that heat treatment of serum samples (in a heat block at 103°C for 10 minutes, the resultant coagulum centrifuged, and the supernatant used in each commercial assay) may increase the sensitivity of antigen tests in cats by disrupting immune complexes that are often found in infected cats (Antigen masking). Some laboratories are now offering this service that could be useful in case of strong suspicion (i.e. antibody positive cats with no echocardiographic evidence ow adult worms).

Test for antibodies to adult heartworm

Due to the low sensitivity of tests for circulating microfilariae and adult antigens in cats, tests for detection of antibodies to adult heartworm can be useful to decrease the index of suspicion, and can be specifically very helpful in case of HARD as they are the only test that can be positive 3-4 months post infection.

Antibody tests have high sensitivity, but only moderate specificity due to cross reactivity with other parasites or due to the presence of antibodies to abortive infections. Sensitivity is high in recent infections and decreases with the time due the reduced antibody response. Consequently, antibody tests should be interpreted carefully, taking other relevant clinical information into consideration.

Treatment

To date, there are no studies that indicate any form of medical adulticidal therapy increases the survival rate of cats harbouring adult heartworms

For these reasons and because heartworm infection in cats is often self-limiting, infected cats are managed only with supportive treatment, although conservative management is not without risk, as the acute death syndrome may occur without premonitory signs and in the presence of only one worm.

Due to incomplete sensitivity of tests for the detection of antigens and antibodies, using both is strongly advised for screening cats. If both are negative infection is unlikely. If one of them is positive see below

Symptomatic cats

Antibody test	POS	**Cat infected**					
Antigen test	POS						
Antibody test	NEG	**Cat infected**					
Antigen test	POS						
Antibody test	POS	High suspicion Plan Echocardiography	POS	Cat infected			
Antigen test	NEG		NEG	Possible HARD or Antigen masking	Ask for Antigen test on heat treated serum sample	POS	**Cat infected**
						NEG	Monitor the cat and recheck 4 months later

Wait and see

Medical treatment of feline heartworm disease is typically symptomatic. Indeed, specific, adulticidal therapy is associated with a high rate of complications. Furthermore, cats frequently self-cure. Therefore, if a cat does not show clinical signs or radiographic evidence of pulmonary vascular/interstitial lung disease consistent with the infection, the best choice seems to allow time for a spontaneous self-cure to occur.

These asymptomatic cases must be monitored periodically every 4-6 months by repeating antibody and antigen testing, thoracic radiography and echocardiography.

Corticosteroids

Injectable prednisolone administered at 2 mg/kg, tapering down over a four-week period, is effective medical support for infected cats with radiographic evidence of lung disease whether or not they appear ill. This treatment has to be repeated in cats with recurrent clinical signs. Oral administration of prednisone in cats is not advised due to decreased hepatic conversion of prednisone to prednisolone and injectable corticosteroids are preferred because of variability of gastrointestinal absorption. In some cases following the acute treatment or in cats with recurrent clinical signs the administration of lasting corticosteroids (methylprednisolone acetate, 20 mg s.c. cat once in a month) may be a reasonable choice.

Cats with severe clinical signs of heartworm disease should be stabilized by administration of intravenous fluids, intravenous corticosteroids, bronchodilators and oxygen supplementation. Diuretics should be absolutely avoided, even if radiographs show severe interstitial or patchy alveolar lung patterns. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have failed to produce any benefit and may exacerbate the parenchymal pulmonary disease. Once stabilized, treatment can continue as described above based on clinical signs.

Adulticide treatment

Pharmacological elimination of adult parasites is associated with significant risk and is considered the last resort for cats in unstable condition with clinical signs that are not controlled by corticosteroids.

Melarsomine dihydrochloride treatment is not recommended for use in cats. Data suggests that melarsomine is toxic to cats at doses as low as 3.5 mg/kg and that its efficacy is only about 36% against adult heartworms in cats. Ivermectin at a dose of 24 µg/kg monthly given for 2 years has been reported to reduce worm burdens by 65% as compared with untreated cats. In cats it is not the worm mass alone that is dangerous but the "anaphylactic" type reaction resulting when even a single worm dies, this will likely also occur when the ivermectin-treated worms die but the severity of the reaction is unknown.

There is still debate on the usefulness of doxycycline in infected cats in order to target *Wolbachia*. It is not known if it has the same beneficial effect as has been reported in dogs and there is no data on the adulticidal effect of the macrocyclic lactone/doxycycline combination in cats. Therefore, doxycycline is not recommended as an adjunctive therapy in cats at this time.

Minimally invasive Surgical Heartworm removal

Surgical removal of heartworms may be attempted in symptomatic cats when the parasites are echocardiographically visualized in the right heart and main pulmonary arteries, with thin horsehair brush or basket catheters or other intravascular retrieval snare introduced via the right jugular vein into the right cardiac chambers. Surgical extraction of worms can also be attempted via thoracotomy and right atriotomy or ventriculotomy and main pulmonary arteriotomy for removing them from pulmonary arteries. Care should be taken to remove worms intact, because the frequent accidental damage to worms during extraction can result in acute circulatory collapse and death mainly when parasites are removed via jugular vein because the small size of the vessel compared to the worms. The incidental rupture of worms during the procedure may result in the dead of the cat (till 30% of cases). Heartworm surgical removal in cats for this reason is not considered in cats as safe as in dogs.

Prognosis

The prognosis for heartworm-infected cats should be considered guarded. Approximately 80% of naturally

TABLE 1 - MACROCYCLIC LACTONES USED FOR THE PREVENTION OF FELINE HWD

Drug	Administration	Dose	Interval	Efficacy against other ESDA parasites #
Ivermectin	Oral	24 mg/kg	Monthly	*D. repens*
Milbemycin	Oral	2 mg/kg	Monthly	
Selamectin	Spot on	6 mg/kg	Monthly	
Moxidectin	Spot on	1 mg/kg	Monthly	*D. repens*
Eprinomectin	Spot on	0.48 mg/kg	Monthly	

infected cats self-cure and 20% die often very suddenly. Prognosis is better for cats surviving beyond the day of presentation.

Prevention

The best approach to feline heartworm disease is prevention through the regular monthly administration of drugs that kill the infective larvae in the L3-L4 stage. Monthly heartworm preventives are a safe and effective option for cats living in or travelling to areas where heartworm infection is considered endemic in dogs and exposure to infective mosquitoes is possible. Even the so-called "indoor" cats may also be considered at risk, even in low endemic areas. When monthly heartworm prevention is chosen, it should at least be administered within 30 days following the estimated onset of transmission and continued within 30 to 90 days after that period has ended. 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.

There are currently five macrocyclic lactone drugs registered for feline heartworm prophylaxis, alone or in combination with other active principles (see Table 1).

Additionally, depending on the active ingredients, these products protect cats from a variety of common endo- and ectoparasitic infections.

These drugs can be administered in cats that are antigen/antibody positive. Therefore, screening of cats before administration is less useful than in dogs. Many, if not most, cats that are antibody positive have only been transiently infected to the L4 stage and antibody positivity confirms the potential risk of developing HARD and giving more justification for recommending preventives.

Given the incomplete sensitivity of tests in cats, testing before starting prevention in adult cats is suggested, but not mandatory.