

Dirofilaria immitis (heartworm)
Management in Canine
Patients

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Objectives

- Discuss the prevalence and pathophysiology of *Dirofilaria immitis* infection
- Review signs and symptoms of infection
- Discuss testing and diagnostic methods for *Dirofilaria*
- Discuss the prevention and treatment options for infection in dogs
- Analyze the primary literature regarding future treatments

Heartworm

- Infection caused by *Dirofilaria immitis*, a parasitic roundworm (*Nematoda*)
- *Wolbachia* co-infection
- Life cycle:
 - Five stages (L1-L5) and four molts
 - Adult (L5) by three months
 - Grow up to 30cm (12") long
 - Dogs develop microfilaria at 6-7 months, which live 5-7 years
 - *Vector*: mosquito

AHS, 2009

CAPC,

2009

Canine heartworm Life Cycle

As a mosquito feeds, infective larvae escape from its mouthparts into a drop of hemolymph, later entering the wound.



Larvae develop within tissues and begin migration to the heart. (Ivermectin eliminates the tissue stage - breaking the life cycle before larvae develop into adult worms.)

After 2-3 weeks, microfilariae develop into infective larvae within the mosquito.



Mosquito ingests microfilariae while sucking blood from an infected dog.



Approximately four months later, young adult worms are present in the heart and pulmonary arteries.



By six months, adult female heartworms can shed microfilariae in the blood stream.

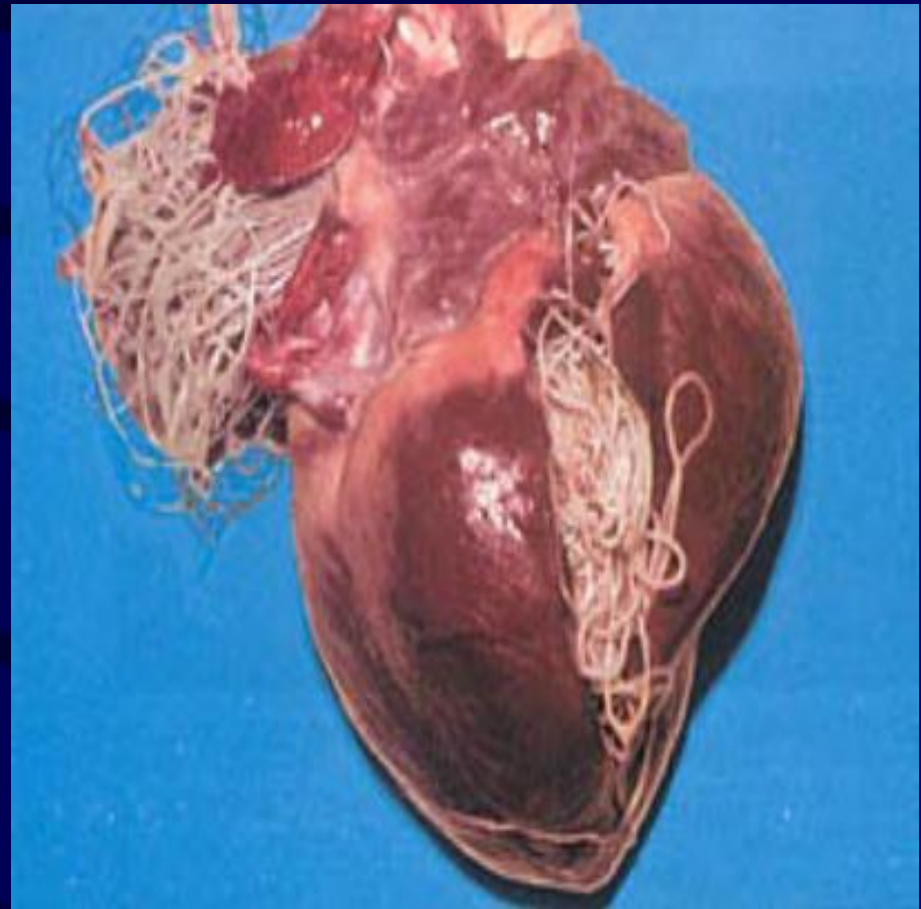


Prevalence

- Endemic 49 states and all US territories
- Climate
 - $>64^{\circ}$ for at least one month
 - Heat necessary for larvae maturation
 - Need heat for survival of mosquitoes
 - $<57^{\circ}$ for several hours slows maturation
- Transmission
 - Southern Florida: All year
 - Southern Canada: Less than four months

Pathophysiology

- Arteries of lungs and right side of heart affected
 - Pulmonary embolism
 - Pulmonary hypertension
 - Right-sided heart failure
- Hematologic changes
 - Anemia
 - Thrombocytopenia
 - Eosinophilia



<http://olddominionvet.com>

^m CAPC,
2009

Pathophysiology

- *Class I:* Asymptomatic or mild; no clinical or radiographic signs, no laboratory abnormalities.
- *Class II:* Moderate; Occasional cough, exercise intolerance, increased lung sounds, radiographic changes.
- *Class III:* Severe; anemia, weight loss, exercise intolerance, dyspnea, ascites. Radiographic changes show right ventricular hypertrophy and pulmonary arterial changes
- *Class IV (Caval syndrome):* Life-threatening; sudden onset of collapse, hemoglobinuria, and respiratory distress

Signs and Symptoms

- Lethargy
- Exercise intolerance
- Reduced appetite and weight loss
- Mild, persistent cough

Clinical Management: Testing

Heartworm Testing

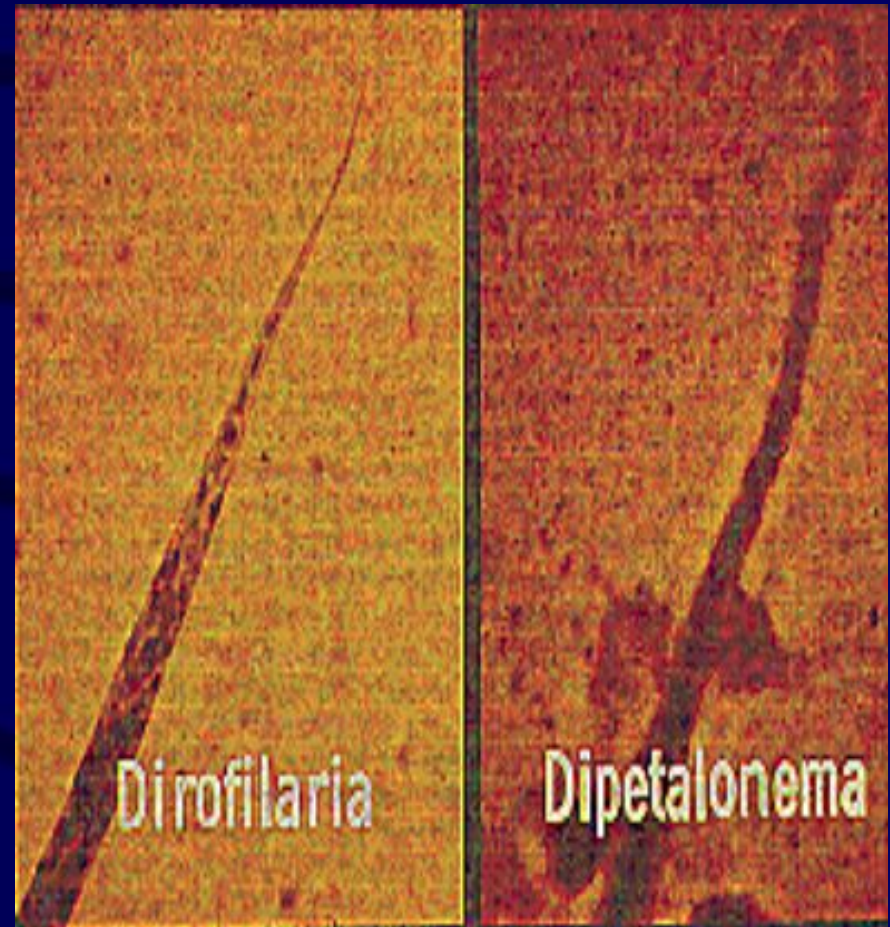
- Testing Methods:
 - Antigen
 - Microfilaria
- Earliest detection is five months post-infection
- Dogs born out of heartworm transmission season don't need testing prior to preventative treatment
- **Timing: seven months after end of season**

Antigen Testing

- Mechanisms
 - ELISA
 - Immunochromatography
- Test for mature female heartworms
- High (~100%) specificity
- Used as the initial screening tool

Microfilaria Testing

- Knott test: Standard technique
 - Concentration technique
 - Differential diagnosis
 - Morphology, body dimensions
 - Non-pathogenic filaria: *Acanthocheilonema* (formerly *Dipetalonema*) *reconditum*



<http://marvistavet.com>

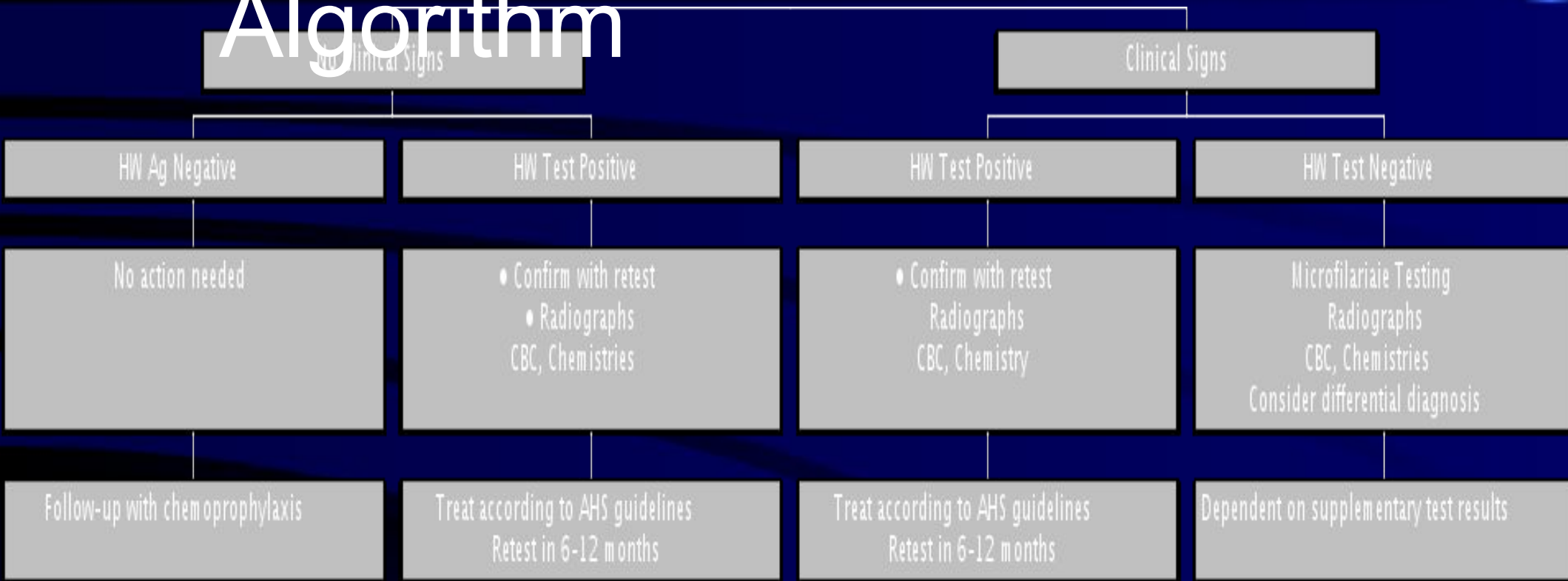
AHS,
2009

Diagnostic Aids

- Radiographic Evidence
 - Assess severity
 - Enlarged right ventricle
 - Pulmonary arterial changes
- Echocardiography
 - Assess changes in heart function
 - Echo from heartworm body wall detected on ECG

Heartworm Testing

Algorithm



Idexx,
2009

Clinical Management: Prevention

Prevention

- All dogs must test negative for *Dirofilaria* before preventive is started
- Preventive Options:
 - Macrocyclic lactones: Hyperpolarizes nerve and muscle cell action potentials in susceptible organisms
 - Ivermectin
 - Milbemycin
 - Selamectin
 - Moxidectin
 - Diethylcarbamazine citrate: Exact mechanism unknown; thought to act as a nicotine agonist
AHS, 2009; Plumb, 2005

Collie Sensitivity

- Breed-specific sensitivity to macrocytic lactones
- Genetic variant
 - MDR-1 (wildtype): 20% of Collies
 - mdr1-1 (mutant): Defect in P-glycoprotein
- All macrocytic lactones are substrates of P-glycoprotein

Ivermectin (Heartgard, Iver-Heart, Tri-Heart)

- **Dosing Guidelines:** 6mcg/kg (2.72mcg/lb) once monthly during transmission season
 - 68mcg, 136mcg, 272mcg
- **Precautions:**
 - **Pregnancy/Lactation:** Safe in pregnancy
- **Adverse Reactions:** mydriasis, ataxia, vomiting, diarrhea, hypersalivation
- **Drug Interactions:** None known
- **Contraindications:** Positive heartworm test, <6 weeks old

Merial, 1989

Lexi-Comp,

2009

Milbemycin (Interceptor)

- **Dosing Guidelines:** 0.5mg/kg (0.23mg/lb) once a month
 - 2.3mg, 5.75mg, 11.5mg, 23mg tablets
- **Precautions:**
 - **Pregnancy/Lactation:** Safe in pregnancy
- **Adverse Reactions:** ataxia, vomiting, diarrhea, hypersalivation, convulsions, weakness
- **Drug Interactions:** none known
- **Contraindications:** Positive heartworm test, <4 weeks old, <2lbs,

Plumb,
2005

Selamectin (Revolution)

- **Dosing Guidelines:** 6mg/kg (2.7mg/lb) topically once a month
- **Precautions:** Sick, debilitated, or underweight animals
 - **Pregnancy/Lactation:** Safe in pregnancy
- **Adverse Reactions:** Diarrhea, vomiting, anorexia, lethargy
- **Drug Interactions:** none known
- **Contraindications:** Positive heartworm test, <6 weeks old

Plumb

2005

Moxidectin (Proheart 6, Advantage Multi)

- **Dosing Guidelines:** 0.17mg/kg Scut every six months.
 - Do not inject more than 3mL per site
- **Brand Names:** Proheart 6, Advantage Multi
- **Precautions:** Sick or debilitated animals
 - **Pregnancy/Lactation:** Safe in pregnancy and lactation
- **Adverse Reactions:** Lethargy, ataxia, anorexia, diarrhea
- **Drug Interactions:** none known Plumb, 2005
- **Contraindications:** Positive heartworm test Fort Dodge, 2008

Clinical Management: Treatment

Treatment

- *Melarsomine*: Arsenic compound used for Class I-III infections
- *Ivermectin*: Used as an adjunct to melarsomine
- *Surgery*: Necessary for Class IV heartworm infection

Merck,

2009

AHS, 2009

Melarsomine (Immiticide)

- **Dosing Guidelines:** Given by deep IM injection
 - Class I/II: 2.5mg/kg IM twice, 24 hours apart. Symptomatic treatment if necessary
 - Class III: 2.5mg/kg once, then again one month later. Rest and symptomatic treatment
- **Precautions:**
 - **Pregnancy/Lactation:** Safety not established in pregnancy
- **Adverse Reactions:** Injection site pain, firm nodules at injection site, coughing, lethargy/depression, lack of appetite, fever, vomiting
- **Drug Interactions:** Drugs that potentiate adverse effects
- **Contraindications:** Class IV heartworm infection

Ivermectin

- Used for one to six months prior to treatment with melarsomine
- Thought to reduce risk of pulmonary embolism by:
 - Reducing circulating microfilarae
 - Stunt growth of immature heartworms
 - Reduce female worm mass by destroying reproductive system

Merck,
2009

Surgery

- Absolutely necessary in Class IV *Dirofilaria* infection
- Involves removal of heartworms from the heart, including right atrium and pulmonary circulation
- Follow-up treatment with melarsomine necessary within a few weeks

Merck,
2009

Investigational Treatments

Combined ivermectin and doxycycline treatment has microfilaricidal and adulticidal activity against *Dirofilaria immitis* in experimentally infected dogs

Bazzocchi et Al.
Int J Parasit 2008

Study Design

- Total of 20 beagles experimentally infected with *Dirofilaria*
- Treatment Arms:
 - Ivermectin (IVM)
 - Doxycycline (DOX)
 - Ivermectin + Doxycycline (IVM+DOX)
 - Control
- Knott's test for microfilariae (mf)
- PCR for *Wolbachia* population estimates
- Necropsy at 36 weeks

Bazzocchi,
2008

Results and Conclusions

- 100% of IVM+DOX were amicrofilaremic at 12 weeks
 - Most in IVM and DOX still had mf at necropsy
- IVM+DOX adulticidal rate 78%
 - IVM: 20%
 - DOX: 9%
- IVM+DOX is superior to either agent alone in the treatment of *Dirofilaria* infections

Bazzocchi,

2008

Limitations

- Treatment arms weren't compared to gold standard melarsomine
- Small sample size
- Only one breed (Beagle) was studied

Bazzocchi,
2008

Summary

- *Dirofilaria immitis* is a global disease strongly correlated with climate
- Preventative management is a key factor in controlling the disease and includes the use of macrocyclic lactones and DEC
- Treatment with melarsomine is indicated for Class I-III, with ivermectin as an adjunct
- Surgery is necessary to treat Class IV infection
- Doxycycline provides promise for treatment in the future

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