Some topics related to heartworm disease leave themselves open to scientific interpretation; therefore, the slides in this PDF presentation are a general consensus for the purpose of presenting only and may not necessarily reflect various personal opinions of the speakers. We are providing slides as a general outline of the presentation but the order may vary. In addition, because HWU continues to be enhanced, some slides may be added or deleted by the speakers prior to the presentation.

No written notes will be provided the day of the event.

Heartworms
Antigen to Zoonosis
Heartworm University

The American Heartworm Society

www.heartwormsociety.org

• The mission of the American Heartworm Society is to be the global resource for the prevention, diagnosis, and treatment of heartworm disease.

• Objectives
  - Further scientific progress in the study of heartworm disease
  - Inform our more than 1,000 members—veterinary practitioners, researchers, libraries, and industry partners—of new developments
  - Promote effective procedures for the diagnosis, treatment, and prevention of heartworm disease

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Heartworm University: Curriculum

- Prevalence and Epidemiology
- Heartworm Disease and Complications
- Diagnosis of Heartworm Infection
- Heartworm Treatment and Prevention
- Case Examples
- Controversies in Heartworm Disease

Heartworm Infection: Solving the Puzzle

- The Parasite
  - Prevalences/challenge rates
  - Developmental cycle (where are they and when?)
  - Role of intermediate hosts (species and abundance?)
- The Preventives and Adulticide(s)
  - What they eliminate, when and how
- The Diagnostic tests
  - What they detect and when
  - Performance characteristics

Dirofilaria immitis

THE CRUEL FILARID
The genus Dirofilaria currently contains 27 species in two subgenera
- Dirofilaria Dirofilaria immitis is one of the members of the subgenus found in the heart of the host
- Dirofilaria Nochtiella repens is the well known subcutaneous filarid of dogs in Europe
- Acanthocheilonema (Dipetelonema) reconditum is a subcutaneous filarid of dogs in US and beyond

Heartworm Worldwide

Heartworm Disease: Terminology

- L1 = microfilariae (Mff); some call these pre-larvae
- L5 = adults
- Early L5 = immatures (young or immature adults)
- Mature L5 = mature adults

Terms and Definitions

- Precordial (Larval) Heartworms
  - Worms en route to the heart
  - Age: generally from L3 in cutaneous tissues to about 70 days (L4; early L5)
  - Not detectable with canine tests
  - Likely to be killed by single doses of preventives (may depend on product)
  - Maturation inhibited by multiple doses of preventative
Terms and Definitions

- **Sub-adult (Immature) Heartworm**
  - Reproductively immature
  - Age: generally > 70 days but < 150 days
  - Generally not detectable with antigen tests
  - May not be affected by single doses of preventives (may depend on product)
  - Can be affected by multiple doses of preventives (varies with preventive)

- **Mature or Adult Heartworm**
  - Reproductively active
  - Detectable with antigen tests (female only; if sufficient antigen is present)
  - Age: generally ≥ 6 months (normally 6-8 months)
  - Microfilariae production and release begins at about 6 months, but may be delayed for days or weeks

**Dirofilaria immitis**

**Identification**
- Adults are long, slender white worms
- Males are 5 to 7 inches
  - Males have corkscrew-like tail
- Females are 10 to 12 inches

**Diagrammatic Life Cycle of Dirofilaria immitis (Dogs)**

- Mosquito feeds on dog with circulating microfilariae

**Dirofilaria immitis (Bottom)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Measurement</th>
<th>Dipetalonema reconditum (Top) (Acanthocheilonema)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length:</td>
<td>307 to 322 μm (Avg. 310)</td>
<td>246 to 293 μm (Avg. 280)</td>
</tr>
<tr>
<td>Width:</td>
<td>6.7 to 7.0 μm</td>
<td>4.7 to 5.8 μm</td>
</tr>
<tr>
<td>(1/3 from anterior end; see above)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shape of head:</td>
<td>Tapered</td>
<td>Blunted</td>
</tr>
<tr>
<td>Cellularity of anterior end</td>
<td>Cellular</td>
<td>Clear space</td>
</tr>
<tr>
<td>Condition of tail</td>
<td>Straight</td>
<td>Button hook shape in some (artifact of formalin fixation)</td>
</tr>
</tbody>
</table>
Heartworm and Mosquitoes

- Mosquito vectors:
  - L3 have been shown to develop in at least 70 species (laboratory conditions) (Otto)
  - At least 23 species can transmit heartworm (Scoles, 1998)
  - At least 14 species of mosquitoes are common vectors (Scoles, 1998, plus recently Tiger and Egyptian species)
  - Distribution of mosquito species is highly variable
  - Feeding habits of mosquitoes also variable (i.e., dogs and wild canids, cats, humans)
- Breeding sites vary among mosquito species
  - Aquatic environments
  - Flood plains
  - Tree holes

Mosquito Preference: Dog vs. Cat

Breeding sites vary among mosquito species

- Aquatic environments
- Flood plains
- Tree holes

Diagrammatic Life Cycle of Dirofilaria immitis (Dogs)

1. Mosquito feeds on dog with circulating microfilariae (15-18 species 14 are common vectors)
2. Microfilariae develop to infective larvae (temperature dependent)

Heartworm Transmission

- Female feeding
- Female transmitting L3

Seasonality and Heartworm Development Units (HDUs)

- Slocombe, Lok, and Knight developed maps with isolines for US
- Similar to showing when to plant different garden plots
- Similar to showing when to treat for bots
- Based on timing of development of larvae inside mosquitoes at a given temperature
  - Lok & Knight, 1995 Proc Am Heartworm Soc, 37-42
**Predicted HDUs**

Time to Attain 130 HDU @ Various Average Temperatures

<table>
<thead>
<tr>
<th>TEMPERATURE</th>
<th>TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>15°C (59°F)</td>
<td>130 days</td>
</tr>
<tr>
<td>17°C (62°F)</td>
<td>43 days</td>
</tr>
<tr>
<td>20°C (68°F)</td>
<td>1 month</td>
</tr>
<tr>
<td>24°C (75°F)</td>
<td>13 days</td>
</tr>
<tr>
<td>30°C (86°F)</td>
<td>8 days</td>
</tr>
<tr>
<td>32°C (89°F)</td>
<td>1 week</td>
</tr>
</tbody>
</table>

**Lok-Knight Heartworm Transmission Model**

- Macroplus heartworm chemoprophylaxis estimated timing of first monthly dose 1st day of month administration
- Macroplus heartworm chemoprophylaxis estimated timing of last monthly dose 1st day of month administration

- 200 weather stations throughout USA
- >30 years of consecutive temperature data
- Worst case scenario for HW transmission
- In northern half of the US, preventative “needed” only 4-5 months.

**Arguments Against Seasonal Prevention**

- HW remains prevalent
- HW continues to spread geographically
- Compliance remains poor
- Microclimates exist
- Achieve reachback and adulticidal benefits only with year-round preventative
- Other parasites (and zoonotic disease) also prevented
- CAPC recommends this practice

- Year-Round Prevention is Advisable

**Heartworm Infection: Seasonal Effects**

*McTier, et al, AHS, 1992*

<table>
<thead>
<tr>
<th>Month</th>
<th>Percent Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Mos</td>
<td>96</td>
</tr>
<tr>
<td>April-Aug</td>
<td>84</td>
</tr>
<tr>
<td>Aug-Dec</td>
<td>74</td>
</tr>
<tr>
<td>Dec-April</td>
<td>9</td>
</tr>
</tbody>
</table>

**Diagrammatic Life Cycle of Dirofilaria immitis (Dogs)**

1. Mosquito feeds on dog with circulating microfilariae
2. Microfilariae develop to infective larvae (temperature dependent)
3. Infective larvae are deposited at the skin surface when mosquito takes another blood meal. Larvae enter the mosquito bite "wound"
4. Larvae undergo several molts during their migration to the heart and lungs
5. Adults worms mature in the heart or lungs, mate, and produce microfilariae

Prepatent period = 5.5 - 7 months

**Larval Stages Recovered**

- L3 to L4: 3-6 days
- L4 to immature adult: 50-70 days

*Kotani & Powers, AVJR 43:2199-2206, 1982*
So, a Question

- On your first day in Moose Jaw, Canada, your employer finds that his birddog Rufus, just purchased and flown from Charleston, SC, is microfilaremic on the Knott’s test.
- Rufus is a just-weaned male German short-hair pointer.
- Your boss has little experience with heartworm infection, is irritated, and asks your advice.

In Dogs

- Heartworms have been diagnosed in all 50 of the United States and its territories
- Heartworms are at least regionally endemic in each of the contiguous 48 states, Hawaii, Puerto Rico, Virgin Islands, and Guam
- Heartworm transmission has not been documented in Alaska
Heartworms Remain!
Dogs test positive for heartworms
AHS Survey 2004

New York
2,519
Massachusetts
1,807
Michigan
5,209
North Carolina
37,511
Florida
32,138

Data Courtesy of The American Heartworm Society

More than 250,000 heartworm-positive dogs
Positive dogs in all states including Alaska and Hawaii

Heartworm by regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Positive</th>
<th># Tests</th>
<th>% Pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midwest</td>
<td>8,415</td>
<td>1,039,205</td>
<td>0.8%</td>
</tr>
<tr>
<td>Northeast</td>
<td>4,039</td>
<td>707,875</td>
<td>0.6%</td>
</tr>
<tr>
<td>Southeast</td>
<td>20,072</td>
<td>515,157</td>
<td>3.9%</td>
</tr>
<tr>
<td>West</td>
<td>10,972</td>
<td>920,287</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Wild Vectors: Coyotes
The range of the coyote has expanded eastwardly in the last 50 years
At the same time, heartworms have spread in this reservoir host
(Sacks et al., 2003)
In California:
Coastal Range foothills – increase: 10% to 44%
San Francisco foothills – increase: 8% to 32%
In other areas, coyotes are infected at fairly high levels
16% of the coyotes statewide in Illinois (Nelson et al, 2003)
43% of coyotes examined in a survey in Florida (Foster et al, 2003)

Heartworm in California

Sacramento County
Canine
Coyote

Heartworm Spread: Using MN as an Example
(Stromberg et al, AHS 1995)
In Cats

- Heartworm-positive cats have not been found in all 50 states

However...

IDEXX Ref Laboratory Prevalence Study

Feline Heartworm

Zip codes representing clinics requesting feline HW antibody tests

IDEXX Ref Laboratory Prevalence Study

Feline Heartworm

Zip codes representing clinics requesting feline HW antigen tests

IDEXX Ref Laboratory Prevalence Study

Feline Heartworm

Zip codes representing clinics that obtained at least one antibody positive result

Necropsy-Based Prevalence of *D. immitis* in Cats 1939—2004

- * = antigen study
- Median SE USA = 4%
- Mean SE USA = 5.5%

Heartworm Disease

DOGS
CATS
HUMANS
Heartworm Disease in Dogs

Heartworm Disease Manifestations - Dog
- Asymptomatic
- Pulmonary
  - Infiltrate With Eosinophils (PIE)
  - Eosinophilic Granuloma
  - Vascular Disease (PVD)/Hypertension (PHT)
  - Thromboembolism (PTE)
- Congestive Heart Failure (Ascites), Arrhythmias
- Anemia, Thrombocytopenia
- Glomerulonephritis, Proteinuria, Hypoalbuminemia
- Caval Syndrome
- Disseminated Intravascular Coagulation (DIC)
- Sudden Death (rare)

Clinical Signs in Dogs

Potential Physical Exam Findings in Canine Heartworm Disease
- Weight loss
- Pale and/or petechia of mucous membranes
  - Anemia and thrombocytopenia
- Dyspnea and/or cough
  - Pleural effusion, PTE, PIE
- Adventitial lung sounds
  - PIE, PTE
- Ascites, hepato-splenomegaly, jugular distention
  - CHF associated with PHT, TR and atrial fibrillation
- Murmur (tricuspid regurgitation) – uncommon
- Pulses weak, pulse deficits, audible arrhythmias
- Syncope, collapse, exercise intolerance

Heartworm Disease – Pulmonary Infiltrates with Eosinophilia (PIE)

Heartworm Disease: Eosinophilic Pneumonitis (PIE)
Heartworm Disease – Pulmonary Vascular Disease (PVD), Pulmonary Hypertension (PHT)

Physical trauma
Immune mechanisms
Waste products
Altered blood flow
Dying worms

Pulmonary Vascular Disease

Recruitment
Thickened
Dilated
Thrombosed
Fibrotic
Noncompliant
Functionally incompetent
Vasoconstricted

Exercise Intolerance

Pulmonary Hypertension

Thickened
Thrombosed
Fibrotic
Noncompliant
Functionally incompetent
Vasoconstricted

Heartworm Disease – Pulmonary Thromboembolism (PTE)

Spontaneous or Post Adulticide

Heartworm Disease – Congestive Heart Failure (CHF)

Adapted from Rawlings, JAAHA 1978

Not available
Congestive Heart Failure

Determinants of PHT and CHF
- Worm Burden
- Duration of Infection
- Parasite–Host Interaction
- Amount Exercise
- Heart Rhythm
- Tricuspid Valve Function

Heartworm Caval Syndrome

(Atkins, AHS 1998)

Heartworm Caval Syndrome

Heartworm Caval Syndrome

Heartworm Caval Syndrome
Heartworm Caval Syndrome

Glomerulonephritis

Surgical Approach via Jugular Vein

Pitting Edema & Ascites

Cause

- CHF
- Hydrostatic Pressure
- Glomerulonephritis
- Hypoalbuminemia
Aberrant* Heartworm Disease
- Eye (anterior chamber)
- CNS (brain, spinal cord, epidural space)
- Peritoneal cavity
- Subcutis
- Salivary gland
- “Caval syndrome” (RA, vena cavae)
- Systemic circulation
  *Atypical hosts more often suffer aberrant migration

Laboratory Findings Associated with Heartworm Disease in Dogs
- Nonregenerative anemia
- Thrombocytopenia
- Leukocytosis, left shift
- Liver enzyme elevations
- Modified transudate: Abdomen, thorax
- NT Pro-BNP elevation (CHF)
- Proteinuria

Heartworm Disease in Cats

Feline Heartworm Disease - Comparsion to Canine Disease:
- Greater numbers are asymptomatic and self-cure than previously believed (no data on dogs) (Vet Parasitology: Genchi, 2008; Venco, 2008)
- Have an exaggerated pathologic response
- Sudden death more common
- Patient death often associated with worm death
- Pulmonary hypertension/CHF less frequent
- Aberrant migration (arteries, CNS, body cavity) more common
- Vomiting is a sign of HWD

Canine vs. Feline Heartworm (From Blagburn B.L. Veterinary Medicine, Sept., 2000)
- **Canine**
  - Highly susceptible to infection
  - Many worms
  - Disease depends on dog size, no. worms, exercise
  - Worms long lived
  - Usually microfilaremic
  - Heart and lungs affected
  - Generally easily diagnosed
  - Treatment available
  - Preventives available
- **Feline**
  - Less susceptible to infection
  - Few worms
  - Few worms can cause disease
  - **Worms short lived?**
  - Usually amicrofilaremic
  - Lungs most often affected
  - Diagnosis usually requires multiple tests
  - Only symptomatic treatment
  - Preventives available

Life Cycle of *D. immitis* In the Cat:
- Adult heartworms die inciting pulmonary signs and lesions (6-month or longer disease cycle)
- Many *L₄* (immature heartworms) die (90-120 days) inciting pulmonary signs and lesions (3-month disease cycle)
Differential Development (?)

<table>
<thead>
<tr>
<th></th>
<th>Cat</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>180 days</td>
<td>175 days</td>
</tr>
<tr>
<td># Larvae</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td># male/female</td>
<td>10/4</td>
<td>17/15</td>
</tr>
<tr>
<td>Mean Length (M)</td>
<td>3.9 inches</td>
<td>5.1 inches</td>
</tr>
<tr>
<td>(Range)</td>
<td>(3.8-4.1)</td>
<td>(3.9-5.9)</td>
</tr>
<tr>
<td>Mean Length (F)</td>
<td>5.6 inches</td>
<td>8.4 inches</td>
</tr>
<tr>
<td>(Range)</td>
<td>(4.2-7.0)</td>
<td>(5.5-9.8)</td>
</tr>
</tbody>
</table>

Duration of heartworm infection in 43 cats

- Mean = 33.3 months
- Median = 37 months

From Genchi et al., 2008

Feline Dirofilariasis (Mature)

Clinical Signs

N = 50 cats
- DOA
- Neurological
- Vomiting
- Asymptomatic
- Cough
- Dyspnea

(Atkins, JAVMA, 2000)

Heartworm-Associated Respiratory Disease

- HARD

- Vascular and airway disease caused by the early death of immature heartworms in cats
- Caused by unique inflammatory and immunologic environment in the cat lung

Gross Changes: Abbreviated Infection

Cat on Heartworm Prevention
Cat with abbreviated infection

Pathogenesis of FHW Disease (Chronic Tracheitis/Bronchitis??)
Abbreviated Infections

Natural and Experimentally induced Feline HWD

Progression of One-time HARD Infection

Heartworm DX Tests in Cats
Radiographic Diagnosis of Feline Heartworm Disease

- 18 cats infected by the bite of infected mosquitoes (~200 L3)
- Followed sequentially with CXR
- 61% (10/18) - mature HW @ necropsy
- All cats developed pulmonary changes

(Selcer, JVR&S, 1996)

Lesions

- **Group 1:** 79% had occlusive hypertrophy in > 40% of small pulmonary arterioles
  - Correlates to nontreated control cats
- **Group 2:** 50% had occlusive hypertrophy in 20 to 40% small pulmonary arterioles
  - Correlates to abbreviated infections - worms die in lungs
- **Group 3:** 13% had occlusive hypertrophy in < 20% of small pulmonary arterioles
  - Presumably correlates to non-infected controls

Pulmonary Arterial Disease in Cats Seropositive For *Dirofilaria immitis* but Lacking Adult Heartworms In the Heart and Lungs

Leanne E. Browne, DVM; Todd D. Carter, BS; Julie K. Levy, DVM, PhD; Patti S. Snyder, DVM, MS; Calvin M. Johnson, DVM, PhD

American Journal of Veterinary Research

Disease in Humans

Human Heartworm Disease: USA

110 human cases in USA: 1941-2001

Who’s at Risk?

Males 2x females
Outdoorsmen
40–59 years (56%)
Human *D. immitis* Infection

- Coin lesion

**CT scan**

Diagnosis of Heartworm Infection

**Examples of Antigen and Antibody Tests**

- **ELISA**
- **ImChrom**
- **Dirocheck®**
- **PetCheck®**
- **Heska FH®**
- **Heska CH®**
- **Snap® 3DX**
- **Snap® 4DX**
- **Witness HW®**

*Note: Antibody tests are used as an aid in the diagnosis of feline heartworm infections*

The American Heartworm Society recommends dogs be heartworm tested annually.

AHS Guidelines state

- “…antigen testing is the most sensitive diagnostic method”

- “The current generation of heartworm antigen test kits identify most ‘occult’ (microfilaria negative) infections consisting of at least one mature female worm and are 100% specific.”

**When Dogs Become Antigen-Positive**

<table>
<thead>
<tr>
<th>HW age</th>
<th>1m</th>
<th>2m</th>
<th>3m</th>
<th>4m</th>
<th>5m</th>
<th>6m</th>
<th>7m</th>
<th>8m</th>
<th>9m</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrocyclic Lactone Doses Missed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

*Macrocylic lactone prevention (with missed doses) may result in delayed HW maturation and patient conversion to antigen-positive status*
When Dogs Become Microfilaria Positive

<table>
<thead>
<tr>
<th>HW age</th>
<th>1m</th>
<th>2m</th>
<th>3m</th>
<th>4m</th>
<th>5m</th>
<th>6m</th>
<th>7m</th>
<th>8m</th>
<th>9m</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Microfilaria testing can miss ≥20% of heartworm-infected dogs
- The American Heartworm Society recommends using microfilaria testing as an ancillary test for heartworms in dogs

Pets receiving macrocyclic lactones may never develop microfilaria or they may appear only transiently in small numbers

ELISA (Snap®) Test

ELISA Testing Can Bear a Direct But Imprecise Relationship to the Number of Female Heartworms Present

- **Faint Positive**
  - (low Ag, therefore low number of female worms; or early infection with any number of female worms; or dog on ML for several years with sick/dying worms)
- **Positive**
  - (moderate Ag, therefore moderate number of worms)
- **Strong Positive**
  - (high Ag, therefore high number of worms)
  - ELISA testing can be falsely "Strong Positive" if recent heartworm death has occurred

Immunochromatographic (Solo Step™; Witness®) Test

Problems/Issues in Diagnosis (Canine)*

- **Antigen test: Positive**
  - Microfilaria test: Negative
- Maturing infection; microfilariae not yet in circulation
- Macrolide preventive without removing adult worms
- Use of microfilaricide without removal of adult worms
- Unisex (female) infection; males not present
- Dog is a true immune-mediated occult
- Failure to use microfilaria concentration test

*Blagburn, B.L. 2002. Emerging Issues in Heartworm Disease. *DVM In Focus*
Problems/Issues in Diagnosis (Canine)*

- Antigen test: Negative
- Microfilariae test: Positive

1. Microfilariae are those of another species such as *Acanthocheilonema reconditum* or *Dirofilaria striata* (usually low in number)
2. Microfilariae were acquired transplacentally (usually few in number and seen in young dogs)
3. Adult worms were removed or have died but microfilariae persist
4. Contamination of test materials from previous sample

*Blagburn, B.L. 2002. Emerging Issues in Heartworm Disease. DVM In Focus

Problems/Issues in Diagnosis (Canine)*

- Antigen test: Variable
- Microfilariae test: Neg. or Pos.

1. Fluctuating antigen level due to No. of female worms, ages of worms, quality of sample

*Blagburn, B.L. 2002. Emerging Issues in Heartworm Disease. DVM In Focus

Problems/Issues in Diagnosis (Feline)*

- Ag test: Negative  Ab test: Positive
- Microfilariae test: Negative

1. Most common test result; usually due to infection, but failure of larvae to reach maturity
2. Low adult worm burden; cats are transiently microfilaremic or have too few to detect. Some tests by reference laboratories may help to clarify test results
3. Elimination of larvae by preventives
4. Worms at aberrant (ectopic) sites?

*Blagburn, B.L. 2002. Emerging Issues in Heartworm Disease. DVM In Focus

Problems/Issues in Diagnosis (Feline)*

- Ag test: Positive  Ab test: Negative
- Microfilariae test: Negative

1. Cats can lack demonstrable antibody responses, even with confirmed infections
2. Recent data suggests that the number of antibody – negative cats may exceed 1/3 of infected cats

*Blagburn, B.L. 2002. Emerging Issues in Heartworm Disease. DVM In Focus
Problems/Issues in Diagnosis (Feline)*

- Ag test: Negative
- Ab test: Positive
- Microfilariae test: Positive

1. Uncommon. Too few adult female worms to detect. Cat was examined during brief microfilaric phase.
2. Contamination of test materials.

*Blagburn, B.L. 2002. Emerging Issues in Heartworm Disease. DVM In Focus

American Heartworm Society recommends:

- Re-testing when:
  - Pets with signs consistent with heartworm disease test negative
  - Pets in low endemic areas or on preventive medication have weakly positive results

Because of the accuracy of today’s heartworm antigen tests, the American Heartworm Society believes it is better to trust rather than reject test results

The American Heartworm Society recommends:

Antigen testing:
- Pets not yet receiving preventive medication
- Dogs over 7 months of age AND
- 4 months after starting prophylaxis
- Dogs missing doses of preventive medication for more than 3 months
- With seasonal prophylaxis
- At the time of re-initiating prophylaxis

Microfilarial Testing

- Benefits of microfilarial testing:
  - Validate positive antigen test
  - Identify pets serving as reservoirs
  - Predictive of dogs which may react adversely to preventive
  - Rarely a positive occurs in antigen-negative dog (~1%)

Microfilarial Testing

- Methods:
  - Direct smear
  - Capillary tube
  - Modified Knott test
  - Millipore filter test

Thoughts and Recommendations

- Testing:
  - Dogs > 7 mos.; not on prevention
    - Antigen test; Microfilariae test
  - Dogs on prevention but with known (or suspected) lapses in medication (all products)
    - Antigen test yearly; microfilariae test is optional
Thoughts and Recommendations

- **Testing:**
  - Dogs on prevention but with **known long lapses** in medication (all products)
  - Antigen test; microfilariae test
  - Dogs on prevention; good compliant client
    - Clinical judgment (I recommend annual test)
  - Dogs on prevention - switching products
    - Test 4 and 9 months after product switch

Positive Antigen Test:
- Repeat test to confirm POC result (optional?)
- If positive, submit to reference Lab for confirmation
- If reference lab result is positive: recommend treatment

Note: Tests are more specific than they are sensitive (better not to treat an asymptomatic low worm burden dog, than to treat a non-infected false positive dog?)

American Heartworm Society recommends:

Cats that are going to begin chemoprophylaxis should be

SCREENED WITH BOTH AN ANTIBODY AND ANTIGEN DETECTION TEST

Thoracic Radiography
- Can provide strong evidence of HWD
- Caudal lobar pulmonary arteries commonly enlarged
- Enlarged main pulmonary artery is uncommon
- Broncho-interstitial lung disease often apparent
- Cardiac silhouette usually normal
- Hyperinflated lungs with flattened diaphragm
- Less common findings
  - Focal parenchymal radiodensities
  - Consolidated lung lobes
  - Pleural effusion
  - Pneumothorax

Radiographic Findings

PA:R9 < 1.6:1

Schafer, JVR&US, 36, 1995
**Heartworm Disease – Asthma Mimic**

- Bronchovascular Pattern with Hyperinflation

**Heart Failure Due to Heartworm Disease**

- Hydrothorax, often chylous

**Echocardiography**

- Direct observation of heartworms possible and diagnostic
- Worms most commonly found in the main and right pulmonary arteries
- Better chance of finding in the cat because of body size related to worm size
- More likely to identify if multiple worms are present

**Radiographic Findings**
Necropsy Diagnosis May Be Difficult

- Disease may be related to very small immature adults
- Current clinical disease may be related to prior infection
- Small worm fragments may be located in the most distal and very small pulmonary vessels
- Heartworms may be in the brain/spinal canal or body cavities

Examples of Antigen and Antibody* Tests

*Note: Antibody tests are used as an aid in the diagnosis of feline heartworm infections

PREVENTION

Dogs and Cats

Macrocyclic lactones are virtually 100% effective at the prescribed dosing and administration intervals recommended
Macrocyclic Lactones & Microfilariae

- Studies show macrocyclic lactones to be safe to administer to heartworm-infected dogs having no or few microfilariae
- However, dogs with moderate to high numbers should be carefully monitored following administration

Package Insert Information

- Revolution
  - "Hypersensitivity reactions have not been observed in dogs with patent heartworm infections administered three times the recommended dose."
- Advantage Multi for Dogs
  - "Administered at 1X and 5X ... to dogs with adult heartworm infections and circulating microfilariae. Hypersensitivity reactions were not seen in the 5X treatment groups."
- Heartgard Plus Chewables for Dogs (iverhart, Tri-Hart)
  - "A mild hypersensitivity type reaction, presumably due to dead or dying microfilariae and particularly diarrhea, has been observed in clinical trials with ivermectin after treatment of some dogs that have circulating microfilariae."
- Sentinel Flavor Tabs for Dogs
  - "Two studies in heartworm-infected dogs were conducted which demonstrated mild, transient hypersensitivity reactions in treated dogs with high microfilaremia counts."
- ProHeart 6
  - "Caution should be used when administering ProHeart 6 to heartworm-positive dogs."

American Heartworm Society Recommends:

- Starting puppies on prevention no later than 8 weeks of age
- Year-round preventive medication for all dogs
  - In the contiguous 48 continental states
  - Hawaii
  - US territories
  - Protectorates

When Changing Preventive Products

- TESTING Recommended because
  - Identifies product failure
  - Maintains manufacturer guarantee
- Test dogs both 3 and 8 months after changing from one macrocyclic lactone to another
  - If using ProHeart 6, recommend testing 4 to 9 months after changing to another product

Macrocyclic Lactones: “Reach-back”, “Retroactive Efficacy”, “Safety Net”

- When used continuously for 12 consecutive months, these compounds can provide a safety net for missed treatments
- Efficacy varies with compounds
  - The reach-back benefit is considered when there is 95% protection after a 3- or 4-month lapse in preventive administration followed by 12 consecutive months of preventive

HWD Prophylaxis: Compliance

- 22,915 US clinics surveyed
- 9083 responders
- Dogs on preventative: 50%
  - # dogs on prev/# dogs in practice
- Compliance rate: 56.4% (based on sales)
  - # doses/# dogs on prev x (recommended mos)
- Result: 50% x 56.4% = 28.2% coverage

(Merck AgVet, 1997)
HWD Prophylaxis: Compliance

- 80% of dog owners miss giving medication on due date
- 33% of dog owners missed due date by more than 30 days
- 20% of dog owners missed several treatments, and then stopped giving medication all together

(Conducted by KS&R Market Research, August 2000)

Prevention in Cats

- Preventives should be offered to cat owners in any region where dogs are on preventive
- Less than 5% of US cats are on preventive

Heartworm Preventives for Cats

<table>
<thead>
<tr>
<th>Product</th>
<th>Name</th>
<th>Formulation</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartgard® Chewables for Cats (Merial)</td>
<td>Ivermectin</td>
<td>Chewable tablets, given once a month</td>
<td></td>
</tr>
<tr>
<td>Interceptor® Flavor Tabs® for Cats (Novartis)</td>
<td>Milbemycin oxime</td>
<td>Chewable tablets, given once a month</td>
<td></td>
</tr>
<tr>
<td>Advantage Multi™ (D时机)</td>
<td>10% Ivermectin and 1% Moxidectin</td>
<td>Topical spot-on, administered monthly</td>
<td></td>
</tr>
<tr>
<td>Revolution® (Pfizer Animal Health)</td>
<td>Selamectin</td>
<td>Topical spot-on, administered monthly</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT

Dogs

Minimal Pretreatment Assessment

- Heartworm antigen test
- Microfilaria test prior to administering any macrocyclic lactone
- Thoracic radiographs
- CBC/Platelet count/Chemistry panel
- Urinalysis

Pretreatment Assessment

- All pets, with or without signs of disease, should be assessed for their ability to tolerate the effects of adulticide treatment
- Signs requiring attention prior to adulticide treatment include:
  - Congestive heart failure
  - Pulmonary thromboembolism
  - Renal failure
  - Severe hepatic disease
  - Other life-threatening illnesses
Factors Correlating with the Severity of Heartworm Infection

- Strong Ag positivity (ELISA test)
- Visualization of heartworms on echocardiography
- Echocardiology may allow definitive identification of heartworms especially when present in high numbers
- Thoracic radiographs allow the most objective assessment of the severity of cardiopulmonary disease related to heartworm infection
- But mild changes do not preclude serious adverse reaction to adulticidal therapy
- Owners’ failure to restrict pet’s exercise

Variables Most Predictive of Post-adulticidal Complications

- Heavy worm burden
- Radiographic evidence of cardiopulmonary disease
- Owner’s ability or willingness to restrict exercise
- Symptomatic heartworm disease

Dogs - Therapy of HW Infection

- Adulticidal therapy
  - Melarsomine
  - Ivermectin “soft-kill”
  - Surgical removal
- Microfilaricidal therapy
- Ancillary therapy
  - Corticosteroids
  - Doxycycline
  - Aspirin?
- Specific “Syndromes”
  - Asymptomatic
  - PIE/Eosinophilic granuloma
  - PTE
  - CHF/PHT
  - Caval syndrome
  - Glomerulonephritis

Adulticide Therapy

Immiticide is the only adulticidal heartworm treatment recommended by the American Heartworm Society

American Heartworm Society recommends:

The three-injection or “split” protocol for all canine heartworm treatments
Macrocyclic lactones should be initiated at the time of heartworm diagnosis as recommended by the American Heartworm Society.

Exercise restriction for all dogs diagnosed with heartworms starting at the time of diagnosis and continuing 4 to 6 weeks post adulticide treatment is also recommended.

**Melarsomine (Immiticide)**

- 1 IM dose (2.5 mg/kg) f/b 2 doses over 24 hours apart @ 1 month (split dosage)
- Flexible dosing schedule allows slower kill rate and ability to alter protocol if adverse reaction
- Highly efficacious
- Fewer side effects:
  1. 33% injection site inflammation
  2. 27% cough (PTE)

**Avoiding Melarsomine Complications: Local Inflammation**

- Double-check dosage
- Change needle after drawing up medication
  - Up to 10 kg – 23 g, 1 inch
  - >10 kg – 22 g, 1.5 inch
  - Giant breeds, two sites
- Locate site, deep, quick IM insertion
- No injection until placed
- Aspirate, inject all
- Apply pressure
- Record site & alternate
- Consider NSAID, steroids

**Avoid Exercise**

No-No!
Ivermectin as Adulticide: Further Studies

- Three groups (n=5) beagles given 50 L3 each SQ
- Group 1 = control, Groups 2 & 3 received HeartGard-Plus – beginning at 5 & 7 mos PI
- 10/10 dogs Mf-negative by 14 mos PI
- 9 of 10 treated dogs were Ag-negative @ 31 mos PI
- Adult HW reduced by 98.7% & 94.9% in Groups 2 and 3 (ivermectin/pyrantel) at 36 months
- Ivermectin has 95–99% adulticidal effect if administered continuously for >30 months

Heartworm Disease: Controversies

- Yearly Testing
- Year-round Preventive
- Use of Doxycycline
- Dogs
- Cats
- Glucocorticoid Use
- Delaying Adulticidal Therapy
- Soft-kill of Adults
- Timing of Post-adulticidal Testing
- Management of Cats (Adult HWI, HARD)
- Resistance
- Global Warming – Importance in HWI

Discussion – Slow-Kill

Aspirin: Not an AHS Recommendation

- Theoretical Benefits:
  - Reduce platelet function and hence PTE
  - Reduce inflammation and vasoconstriction
- Studies have varied
  - Reduction in vascular damage, lung disease
  - No improvement in angiographic PA lesions and worsened myointimal proliferation on PM (n=4)
  - HWI increases aspirin dose needed by 50%
    - Increased platelet turnover rate
  - If used, start @ 5mg/kg daily 1-3 wks prior & 4-6 wks after adulticidal therapy

Surgical Removal

- Reduces complications
  - PTE, Caval Syndrome
- Reduces mortality
- Still requires melarsomine
- Carries some risk
  - Other catheters may have less risk of perforation
- Not practical for most

Macrolides: Adulticidal Effects

Ivermectin has 95-99% adulticidal effect if administered continuously for >30 months

(McCall, AHS, 1998)

Heartworm Disease: Controversies

(McCall, AHS, 1998)

Discussion – Slow-Kill

(McCall, AHS, 1998)

Aspirin: Not an AHS Recommendation

(McCall, AHS, 1998)

Surgical Removal

(McCall, AHS, 1998)
American Heartworm Society acknowledges:

The use of preventive dosages rather than microfilaricidal dosages of macrocyclic lactones as an alternative method of elimination of microfilariae after adulticide therapy

American Heartworm Society recommends:

Antigen testing 6 months post adulticide treatment to assess adulticide effectiveness

American Heartworm Society DOES NOT:

support the use of monthly “prophylactic” doses of macrocyclic lactones as an alternative to adulticide treatment

American Heartworm Society recommends:

Use of Prophylactic Macrocyclic Lactones Rather than Adulticide Treatment (“Slow-kill” or “Soft-kill”)

- AHS: “If owners choose prophylactic macrocyclic lactones as an adulticide treatment for their pets, radiographic signs may continue to worsen until all heartworms eventually die.”

Pets receiving macrocyclic lactones in lieu of adulticide treatment should be:
- Exercise restricted until antigen negative
- Evaluated by a veterinarian every 4 to 6 months
- Radiographed every 4 to 6 months to monitor disease progression
- This approach is controversial

American Heartworm Society recommends:

Delaying Adulticidal Therapy

- Delaying adulticidal therapy while macrocyclic lactones are administered
- Benefits and risks need to be considered with regard to individual patient assessment and geography/climate considerations
Dyspneic, Coughing 7-Year-Old
Blue Tick Hound with HW Disease & Murmur

American Heartworm Society acknowledges:

Glucocorticoids during adulticidal treatment
- There may be medical benefits of glucocorticoid treatment during adulticidal therapy
- Based on needs of individual patient
- Effect of glucocorticoids on melarsomine adulticidal efficacy has not been systematically studied
- Clinical impression during years of concomitant use lend increased confidence

Steroids
- Theoretical Benefits:
  - Anti-inflammatory effects for lung & vascular lesions
  - Potential immunosuppressive effect
- Studies
  - Reduction in vascular inflammation
  - Worsening of vascular proliferative lesions & reduced PA blood flow
- Theoretical concerns
  - Reduction in adulticidal efficacy
  - Fluid retention in CHF
  - Steroids are procoagulant

(1. Rawlings, AHS, 1982)

Steroids: Indications
- Pulmonary infiltrate with eosinophils (PIE)
- Pulmonary thromboembolism (PTE)
- Eosinophilic granulomas
- To reduce reaction to melarsomine
- To prevent or treat adverse reaction to preventives in microfilaremic dogs

Steroids: Dosage
- Dosage:
  - Prednisolone @ 1 mg/kg/day for PIE
  - Prednisolone @ 1–2 mg/kg/day for PTE and eosinophilic granuloma
  - Prednisolone @ 1–2 mg/kg/day – prevention of reaction to treatments
- Treatment of reaction:
  - Intravenous - prednisolone sodium succinate or dexamethasone @ shock dosages
  - Intravenous fluids @ shock dosages

American Heartworm Society acknowledges:

Doxycycline as part of a pre-adulticidal protocol
- There is inadequate data to support conclusive recommendations at this time
Doxycycline

- In 1975, bacteria-like organisms were observed with EM in microfilariae and developing embryos of *Dirofilaria immitis* (McLaren et al, 1975)
- Later shown to be similar to *Rickettsia*-like *Wolbachia* endosymbionts of arthropods (Bandi et al, 1995)
- Tetracycline Rx of cattle with *Onchocerca* resulted in the death of the adult filarial worms, associated with the death of the *Wolbachia* (Langworthy et al, 2000)
- Chronic doxycycline Rx has negative effects on the human filarioid nematodes, *Brugia* & *Onchocerca*
  - But, the long-term and regular administration of these compounds provides no significant advantage over periodic treatment with microfilaricidal ivermectin to prevent transmission (Lammie, 2006)

Wolbachia

- Image of a *D. immitis* microfilaria (in utero) with *Wolbachia* (b)
  - (McLaren, 1976)

Role of Doxycycline in HWI

- **D+I → reduced adults by 78% @ 9 mos**
  - N=30 – 5 grps: I, D, D+I, M, D+I+M, C
  - 16 HW transplanted via jugular vein; Necropsy week 36
  - Treatment
    - Ivermectin/PP preventive (6 µg/kg/week)
    - Doxycycline @ 10 mg/kg/d
      - Weeks 1-6, 10-11, 16-17, 22-25, 28-33 (14 of 36 weeks)
    - Split-dose Imiticide @ week 24
  - Outcome
    - D+I → no mf by ~8 weeks
    - D+I → reduced adults by 78% @ 9 mos
    - D+I+M → no better than M alone but reduces PTE
    - I → reduced adults by 20% & D by 9%

Case 1 – “Shiloh”

**Signalment**

- 3 year-old Blue Tick Hound

**History**

- Owned by this owner for 18 months
- Heartworm preventive history is vague
- Presented today for a laceration on foot-pad
- Upon questioning, owner admits Shiloh has mild cough & possible exercise intolerance
“Shiloh”

- Physical Examination
  - TPR, Wt: 100.1°F, 80 bpm, 24 rpm, 22 kg
  - BAR and thin
  - Pulses normal, no JV distension/pulsation
  - No murmur, gallop or adventitial lung sounds
  - Foot-pad laceration
- Diagnostic work-up (limited by owner, $)
  - HW antigen and microfilaria-positive
  - CBC – normal
  - Chest radiograph

“Shiloh”

- What do you tell owner?
  - Safe to anesthetize and suture foot pad?
  - Prognosis?
  - Best therapeutic approach for HW and Mf?
    - 2-dose melarsomine vs 3-dose vs soft-kill?
    - High-dose macrolide vs preventive dose?
  - Owner has significant money concerns, but wants dog “well” soon so that he can be used for hunting.
    - Owner chose 2-injections over 24 hours

“Shiloh”

- Owner returns 10 days later
  - Shiloh is coughing, has labored breathing
  - Is not eating
  - Cannot keep up with the other dogs during training for hunting season
  - Owner allows only a lateral radiograph

“Shiloh”

- What is the diagnosis?
- What is best therapeutic course here?
- Do you advise hospitalization or home-Rx?
- What is prognosis now?
- Critique case management.
**Case 2 “Duke”**

**Signalment**
- 7 year old M Doberman Pinscher

**History**
- Partial anorexia, cough, distending abdomen
- HW +, microfilaremic
- Treated with lasix, prednisone, doxycycline

---

**“Duke”**

**Physical Examination**
- TPR, Wt: 100.8°F, 140 bpm, 30 rpm, 34 kg
- MM, CRT: pale pink and 2 seconds
- Jugular vein distended and pulsatile
- 3/6 protosystolic murmur right hemithorax
- Increased bronchovesicular sounds
- Ascites
- Systemic BP: 130 mmHg

---

**“Duke”**

**Laboratory Findings**
- Microfilaremic and Antigen-positive
- Leucocytosis, monocytosis, mild eosinophilia
- Abdominal fluid = modified transudate
- Azotemia (BUN = 38 and Cr = 1.7)
- Urinalysis
  - 1.012 USG
  - pH 5.0
  - 2+ proteinuria

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**Case 2 – “Duke” - 7 yo M Doberman**

Ascites, Murmur, Positive HW Ag

---

**“Duke”**

**Echocardiogram**
- RVE, RAE
- TR (mild)
- PHT (60 mmHg)
- HW in main PA
- No DCM
**“Duke” Diagnosis**

- Heartworm Disease
- Microfilaricmic
- Pulmonary Hypertension
- Tricuspid Regurgitation
- Pulmonary Infiltrate with eosinophils
- Right heart failure
- Pre-renal azotemia (normalized with diuretic dosage reduction)

**“Duke” - Treatment**

- Prednisone 0.5 mg/kg q 24 hrs
- Doxycycline 5 mg/kg q 12 hrs
- Furosemide 2.5 mg/kg q 12 hrs (d/c x 7d 1št)
- Enalapril 0.5 mg/kg q 12 hrs
- Pimobendan 0.2 mg/kg q 12 hrs
- Monthly preventive started

  One melarsomine injection given about 1 month later with PTE adverse effects

**“Duke”**

- Owners decline further melarsomine injections
- Furosemide, prednisone, and doxycycline were discontinued over the course of 5 months
- December 2007 meds:
  - Enalapril 0.5 mg/kg q 12 hrs
  - Pimobendan 0.2 mg/kg q 12 hrs
  - Heartgard monthly
- Urine P:C ratio: 1.5
- NT-pro BNP: 47 pg/ml (normal)

**Case 3 “Buster” - History**

- 8 yearold Pit-bull cross
- Poor history of vaccinations and HW preventive
- Slowing down x 3-4 weeks
- Partial anorexia
- No respiratory signs noted
- Abdominal swelling x 1 week
“Buster” – Physical Exam

- TPR: 102°F/180bpm/30 rpm
- MM pink with normal CRT
- No adventitial lung sounds
- Murmur over tricuspid valve
- 4/6 pansystolic, regurgitant quality
- Pulses variable w/ deficits
- Jugular v. distension/pulsation
- Ascites, muscle wasting, and pitting edema

“Buster” – Diagnostics

- What diagnostic tests are indicated?
  - Chest radiographs
  - ECG
  - Echocardiogram
  - CBC
  - HW antigen and modified Knott tests
  - Chemistry Panel
  - Urine analysis
  - Urine protein:creatinine ratio
  - Venous PO2
  - Central venous pressure
  - Abdominocentesis

“Buster” Salient Diagnostic Results

- CBC: mild leucocytosis, eosinophilia
- Antigen-positive and Microfilaria-positive
- Chem: hypoalbuminemia, hypoproteinemia, mild liver enzyme elevations
- Urinalysis: proteinuria 2+ with 1.020 USG
  - Urine protein:creatinine = 2.5
- Abdominal fluid = modified transudate, no neoplastic cells seen

“Buster” Salient Diagnostic Results

- Echocardiogram:
  - RVE, septal flattening, small LV/LA
  - TR with velocity of at least 4 M/sec
  - Trace pulmonic insufficiency – could not measure velocity
  - Large PA with HW evident in PA at bifurcation
  - Chest radiographs
  - Electrocardiogram
“Buster” – Diagnosis?
- Heartworm disease
- Pulmonary hypertension
- RVH & Tricuspid regurgitation
- Atrial fibrillation with rapid ventricular response
- Right heart failure → Ascites, exercise intolerance
- Proteinuria, hypoproteinemia
  - This + hydrostatic pressure → pitting edema

Case 3 “Buster” – Treatment Options
- Furosemide
- Spironolactone
- Sodium restriction (Heart vs Renal Diet)
- Digoxin
- Dobutamine
- Pimobendan (Inodilator)
- Ca channel blocker (Amlodipine, Diltiazem)
- Beta blocker (Carvedilol, Atenolol)
- Nitroglycerin, Hydralazine, Sildenafil (vasodilators)
- Enalapril
- Corticosteroids
- Carnitine, Taurine, Fish oils, CoQ10
- Oxygen
- Immiticide
- Worm extraction
- Euthanasia

TREATMENT
Cats

Feline HWI: Treatment Goals
- Relieve acute signs (usually respiratory)
  - May be due to adult or larval infection
- Rid patient of Adults (possible? advisable?)
- Control chronic signs (respiratory, vomiting)
- Prevent reinfection

CATS – Therapy of HW Infection
- Adulticidal therapy
  - Melarsomine?
  - Ivermectin “soft-kill”
  - Surgical removal
- Microfilaricidal therapy
- Ancillary therapy
  - Corticosteroids
  - Bronchodilators?
  - Doxycycline?
  - Aspirin?
  - Antileukotrienes

There is not definitive therapy for cats, making prevention all the more important!

American Heartworm Society

DOES NOT

- Currently recommend the use of adulticidal treatment in cats
  - No safe adulticidal medication is currently available for cats
  - Death of adult worms often promotes severe clinical disease
Known heartworm-positive cats who are asymptomatic should be evaluated thoroughly every 6 to 12 months
- Repeated antigen and antibody tests
- Thoracic radiographs

**Treatment of Feline HWD**

- When clinical disease is present, supportive and symptomatic treatment may include:
  - Glucocorticoids
  - \(O_2\)
  - Bronchodilators
  - Supportive fluids
  - Ventilator therapy in referral centers
  - Doxycycline?

**Feline Heartworm Disease: Emergency Management**

- IV Steroids
  - Prednisolone Na Succinate - 50-100 mg
  - Dexamethasone - 1 mg

- Oxygen

- Bronchodilators
  - Terbutaline - 0.01 mg/kg SQ or 0.625 mg PO BID
  - Aminophylline – 5 mg/kg IM

**Surgical removal of heartworms**

- Possible if caval syndrome present - jugular approach with alligator forceps or...
- Loop-snare can be used successfully
  - Can reach AVC, PVC, RA, RV in cats
  - Pulmonary artery more difficult
- When in the right ventricle/pulmonary artery, can be removed through ventriculotomy

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