Updates on Heartworm Disease
Brian Patrick, DVM
Bayer Animal Health

Heartworm Developmental Time Table

- L3 (skin; molts to L4 within 3 days)
- L4 (skin, abdomen and thorax; 3-70 days)
- Imm. Adult (lungs) 50-150 days
- Adult (Heart/Lungs) 150+ days

Administer HW Preventives here

Susceptible to HW preventives
HW preventives ineffective

Heartworm Antigen

Antigen Testing
- Tests for an antigen from the adult female heartworm
Antigen Test

- 98 – 100% specificity
  - Positive HW test is probably accurate
  - Retest HW positive dogs on preventives or from hypoendemic areas
  - Retest HW negative dogs exhibiting clinical signs of HW disease
  - Verification samples should be evaluated using a different test platform
  - Presence of Ag does not necessarily mean live worms are present
    - Ag can persist for months after successful adulticidal therapy

Antigen Test

In southern US as many as 5 – 15% of HW antigen tests may be false negative

- Synergistic effect of doxycycline/ML treatment reduces heartworm Ag production
- It is theorized that antigen-antibody complexes can also occur, which render the antigen unavailable for detection
- Production of excess host ‘blocking’ antibody is thought to be associated with chronic inflammation
  - Adulticidal therapy
  - Slow kill

Immune Complex Dissociation

- Heat treatment or low pH break down Ag/Ab complexes
- Extra-label use of test
- Allows heartworm Ag detection in false negative and/or low Ag containing samples
  - Negative Ag test with high index of suspicion of HW disease
  - Adulticidal therapy
  - Positive Ag ≠ live worms are present
- Reduces specificity of test
  - Potential for cross reaction with other parasite species resulting in false positive results
Antigen Test

• Antigen detected in tests is a glycoprotein produced by the adult female heartworm
  — Found predominantly in female reproductive tract
  — False negative possible with low worm numbers

• Not present in absence of adult female heartworm
  — Male only infection
  — Immature infection (less than 6 months old)

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HEAT TREATMENT OF HEARTWORM ANTIGEN TESTS

IMMUNE COMPLEX DISSOCIATION

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Validation of Immune Complex Dissociation Methods for Use with Heartworm Antigen Tests and Utility in Assessing Patient Samples

A.R. Alleman, DVM, PhD, DABVP, DACVP, et al.

Lighthouse Veterinary Consultants, Florida
Heat Treatment of Heartworm Antigen Tests

Background:
• In 2014, Little et al. reported increased prevalence of *D. immitis* antigen in canine and feline serum samples after heat treatment
• Discordant results hypothesized to be the result of immune complex binding of heartworm antigen, rendering it undetectable by Antigen Capture ELISA Tests
  – Excess antibody produced by the host binds heartworm antigen

Little, S., et al., Parasites and Vectors 2014, 7:1

Heat Treatment of Heartworm Antigen Tests

Antigen Capture ELISA Tests
• Positive test result occurs when there is heartworm ‘antigen excess’ in sample
• If host produces excess antibody, it binds free heartworm antigen so there is no available antigen to bind to the test platform
• Exposure to low pH, heat, pepsin or EDTA result in immune complex dissociation allowing accurate antigen detection
  – Early heartworm antigen tests contained immune complex dissociation steps to free heartworm antigen
  – Current commercial heartworm tests no longer contain this step in their protocol

Heat Treatment of Heartworm Antigen Tests

Potential causes of false negative result:
• Increased host heartworm antibody production (host response):
  – Chronic inflammation
  – Worm injury
    • Adulticidal therapy
    • ‘Slow kill’
• Synergistic effect of doxycycline and macrocyclic lactones causes a reduction in heartworm antigen production (parasite response)
Heat Treatment of Heartworm Antigen Tests

Things to consider:

- Heat treatment (immune complex dissociation) improves heartworm antigen detection sensitivity
  - Frees heartworm antigen from immune complexes, reducing the likelihood of false negative results
- Heartworm prevalence study in shelter dogs:
  - 11/154 (7.1%) negative heartworm antigen samples converted to positive after heat treatment

Little, S., et al., Parasites and Vectors (2014)

Heat Treatment of Heartworm Antigen Tests

Things to consider:

- Heat treatment (immune complex dissociation) improves heartworm antigen detection sensitivity
  - May uncover low heartworm burdens
  - Heat treatment may also concentrate antigen levels in sample
  - May allow detection of younger adult worms in certain heartworm isolates

Little, S., et al., Parasites and Vectors 2014

Heat Treatment of Heartworm Antigen Tests

Things to consider:

- Heat treatment of samples constitutes extra-label use of the test
- Heat treatment reduces test specificity (increases the likelihood of a false positive)
  - Antigens from other parasites can cross-react with heartworm antigen test
    - *Dirofilaria repens*, *Angiostrongylus vasorum*, *Spirocerca lupi*
    - *Acanthocheilonema reconditum*, *Dracunculus insignis* (?)

Weisz, L., et al., 2016 American Heartworm Society Triennial Symposium
Heat Treatment of Heartworm Antigen Tests

Things to consider:
- A positive antigen test result does not confirm the presence of live adult heartworms
  - After adult heartworm death, antigen may be present for as long as 6-9 months
- A negative heat-treated antigen test result appears to correlate well with complete adult worm elimination

Savadelis, M., et al., 2016 American Heartworm Society Triennial Symposium Proceedings

Heat Pretreatment of Canine Samples to Evaluate Efficacy of Slow-Kill Treatment

N. V. Labarthe, MV, Dsc, MSc, et al.
Universidade Federal Fluminense, Brazil

Heat Treatment of Heartworm Antigen Tests

Key Points:
- Heat treatment increases test sensitivity
- Heat treatment reduces test specificity and is considered extra-label use
- Heat treatment of heartworm antigen screening tests is not indicated
  - Antigen negative individuals having signs consistent with heartworm disease should be re-tested using heat-treated antigen test to confirm diagnosis
  - Especially important in cats
- Verification of adulticidal efficacy is best accomplished with heat-treated antigen test
  - Timing of test is important
  - 9-12 months post-therapy

Alleman, A.R. et al., 2016 American Heartworm Society Triennial Symposium Proceedings
Heat Pretreatment of Canine Samples to Evaluate Efficacy of Slow Kill Treatment

Background:
- Slow Kill (SK) is the only heartworm treatment available in Brazil
  - Heartworm incidence is extremely high in Brazil
- Recent evidence indicates false negative antigen test results are common when SK therapy is used and that heat-treatment of samples increases antigen detection
- Study was performed to evaluate the interference of SK on diagnostic procedures and the efficacy of heat-treatment in increasing test sensitivity

Methods:
- 19 client owned confirmed HW positive dogs
- Treatment regimen:
  - Macrocyclic lactone monthly
  - Doxycycline 10 mg, bid for first 30 days
- Antigen and mff tested on day 0 and every 6 months thereafter until 2 consecutive negative antigen and mff test results
- Negative antigen tests were heat-treated and re-tested to confirm results
- Dogs released from study when 2 consecutive antigen and mff test results received

Number of Antigen Negative Samples That Became Positive After Heat Treatment

<table>
<thead>
<tr>
<th>Month(s) of SK</th>
<th>6</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen blocked</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1st heated (-)</td>
<td>8</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>2nd heated (-)</td>
<td>0</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Total blocked/Total (-)</td>
<td>6/14</td>
<td>1/21</td>
<td>0/14</td>
</tr>
</tbody>
</table>

Using macrocyclic lactone + Doxycycline treatment protocol:
- All dogs negative for mff at 6 months
- False antigen negatives mainly at 6 months
- At 12 months and after the risk of false negatives is greatly reduced
Heat Pretreatment of Canine Samples to Evaluate Efficacy of Slow Kill Treatment

Conclusions:
• These data suggest slow-kill therapy induces false negative antigen test results, mainly at the 6 months of treatment time point
• After 12 months, the risk of false negative results is sharply reduced, although not eliminated
• These misleading results must be considered by veterinarians when evaluating slow-kill (and probably melarsomine) efficacy

HOW HEARTWORM PREVENTIVES DIFFER

The actives in heartworm preventives are part of the Macroyclic Lactone drug class
All heartworm preventives contain one of the four highlighted drugs

WARNING: DO NOT ADMINISTER THIS PRODUCT ORALLY. For the first 30 minutes after application, ensure that dogs cannot lick the product from application sites on themselves or other treated animals.
How HW Preventives Differ

Unique Pharmacokinetics

Steady-state
Moxidectin Formulation Differences

*The clinical significance of serum levels has not been demonstrated.

CAUTION: Federal (U.S.A.) law restricts Advantage Multi® for Dogs to use by or on the order of a licensed veterinarian.


2 Freedom of Information Summary: NADA 141-251


4 Data on File, Bayer Healthcare, Animal Health

†The clinical significance of serum levels has not been demonstrated.

SUMMARY OF RECENT FINDINGS

A Closer Look at Heartworm Preventives

Heartworm Developmental Time Table

Administer HW Preventive Here

L3 (skin: molts to L4 within 3 days)

L4 (skin, abdomen and thorax; 3-70 days)

Imm. Adult (lungs) 50-150 days

Adult (Heart/Lungs) 150+ days

Susceptible to HW preventives

HW preventives ineffective
Summary of reports indicating lack of efficacy of macrocyclic lactones (ML) for heartworm prevention using SEVERAL challenging strains*

• 1998: CVM first received complaints about ineffective ML products\(^1\)
• 2001: CVM reported an increase in the number of reports indicating lack of efficacy of ML\(^1\)
• 2011-2013: studies sponsored by multiple pharmaceutical companies and conducted by various investigators showed these results
  • Oral ivermectin failed in 4 studies in 31 of 46 dogs\(^2,3,4,5\)
  • Oral milbemycin oxime failed in 6 studies in 28 of 68 dogs\(^2,3,4,6,7\)
  • Injectable moxidectin failed in 1 study in 4 of 4 dogs\(^8\)
  • Topical selamectin failed in 2 studies in 15 of 16 dogs\(^2,4\)
  • Transdermal moxidectin failed in 1 study in 1 of 8 dogs\(^7\)

*Products tested are labeled for ongoing monthly use. The prevalence of MP-3, JYD-34 and JD2009-1 strains of heartworm ... the relevance of these studies cannot be extrapolated to heartworm strains in general. Additional research is needed to determine the prevalence of MP-3-, JYD-34- and JD2009-1-like isolates in the field.

†Animals treated 45 days post infection not included.


Caution: The safe use of this drug has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs body weight.

Summary of reports indicating lack of efficacy of macrocyclic lactones (ML) for heartworm prevention using SEVERAL challenging strains*

• Different HW strains exist
  • At least 3 strains of *D. immitis* tested: MP-3, JYD-34, JD2009-1
  • These challenging strains were sourced from naturally-infected dogs in GA, MO and AR
  • Studies varied in protocol
    • number of dogs
    • consecutive monthly doses administered
    • number of infective larvae used
    • heartworm strain

*Products tested are labeled for ongoing monthly use. The prevalence of the MP-3 strain of heartworm is unknown, so the relevance of this study cannot be extrapolated to heartworm strains in general. Additional research is needed to determine the prevalence of MP-3-like isolates in the field.*\(^1\)


CAUTION. Children should not come in contact with the application sites for two (2) hours after application.

Auburn Study 2011

This was a single-dose laboratory study.
In these laboratory studies, Advantage Multi® for Dogs (imidacloprid + moxidectin) outperformed leading heartworm preventives against the MP-3 and JYD-34 heartworm strains after a single treatment versus one or three treatments for the other products tested, under the conditions of these studies.¹ ² ³

PRECAUTIONS: Use with caution in sick, debilitated, or underweight animals.
Update on Resistance

Using microfilaria from HW infected dogs, MiSeq technology appears to be effective in assessing a heartworm isolate's probable susceptibility or resistance to macrocyclic lactones

- MiSeq technology was used to identify allele frequencies at 40 different loci in both resistant and susceptible heartworm isolates
- 9 SNP (single nucleotide polymorphisms) markers were identified that showed a correlation with resistance
- Represents a multi-focal genetic shift in resistant isolates
- No single, specific genetic marker for ML resistance has been found to date

Pritchard, RK et al. 2016 American Heartworm Society Triennial Symposium Proceedings
Efficacy of Oral Moxidectin in Preventing the Development of Susceptible and Resistant Heartworms in Dogs
T. L. McTier, MS, PhD, et al.
Zoetis, Michigan

Six new heartworm strains were randomly isolated from the field in locations outside the lower Mississippi River region within the past 2-3 years by Zoetis investigators:
- In a Zoetis efficacy study done by McTier et al., three of the six new strains were resistant to oral administration of 3 μg/kg of moxidectin (ProHeart® tablet).
- Four of the new strains showed varying degrees of macrocyclic lactone resistance in separate in vivo studies performed by Prichard et al.

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Update on Resistance

- Oral moxidectin (3 mcg/kg) single dose efficacy against four tested strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>JYD-34</th>
<th>ZoeMO</th>
<th>ZoeLA</th>
<th>AMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>19%</td>
<td>82%</td>
<td>54%</td>
<td>62%</td>
</tr>
</tbody>
</table>

- In another study, 3 monthly doses of oral moxidectin at this same dose were only 44% effective against JYD-34
Update on Resistance

Is there a reproductive fitness ‘cost’ associated with resistance?

- Over time, resistant isolates show genetic drift toward greater macrocyclic lactone susceptibility
  - Shorter worm lifespan?
  - Reduction in microfilaria production?

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PROACTIVE PREVENTION

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Efficacy of Advantage Multi® for Dogs for the Treatment of Heartworm Larvae and the Prevention of Heartworm Infection and Disease All Month Long in Dogs

D.D. Bowman, MS, PhD, DACVM (Hon.), et al.
Cornell University, New York

CAUTION: Federal (U.S.A.) law restricts Advantage Multi® for Dogs to use by or on the order of a licensed veterinarian.
Proactive Heartworm Prevention

Background:

• Most monthly heartworm preventives protect dogs and cats by killing heartworm larvae acquired the month prior to their administration.

• Pharmacokinetic studies indicate that after a single dose of Advantage Multi® for dogs, moxidectin levels remain high enough to kill L3 and L4 for 1 month post-application.

• Are dogs protected from future D. immitis infections after a single dose of Advantage Multi® for Dogs?

Bowman DD, et al., 2016 American Heartworm Society Triennial Symposium Proceedings

The safe use of this drug has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs. body weight.

How HW Preventives Differ

Steady-state

Steady-state serum levels achieved after 4 months*

*Steady state reached after 4 months with continued monthly use of Advantage Multi® for Dogs.

CAUTION: Federal (U.S.A.) law restricts Advantage Multi® for Dogs to use by or on the order of a licensed veterinarian.

WARNING: DO NOT ADMINISTER THIS PRODUCT ORALLY.
Proactive Heartworm Prevention

Methods:
16 dogs were divided into two groups
8 non-treated controls and 8 treated dogs

Protocol timeline:
- Study day -30
- Study day 0
- Study day 148

Protocol timeline:
- Product administration: Advantage Multi® for Dogs; treatment group only
- Infection with 50 L3 HW; both groups
- Necropsy

16 dogs were divided into two groups
8 non-treated controls and 8 treated dogs

Methods:

- CAUTION: Federal (U.S.A.) law restricts Advantage Multi® for Dogs to use by or on the order of a licensed veterinarian.

Results:

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of Animals</th>
<th>Number of Animals with Heartworms</th>
<th>Geometric Mean No. of Worms</th>
<th>Arithmetic Mean No. of Worms</th>
<th>Median No. of Worms</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Advantage Multi®</td>
<td>8</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(2) Non-treated</td>
<td>8</td>
<td>5</td>
<td>6.0</td>
<td>16.8</td>
<td>22.0</td>
</tr>
</tbody>
</table>

Results:

- CAUTION: Federal (U.S.A.) law restricts Advantage Multi® for Dogs to use by or on the order of a licensed veterinarian.

Discussion:
- The results of this study demonstrated that Advantage Multi® for dogs is efficacious for the prevention of heartworm disease and infection all month long with no observation of treatment-related adverse events

Discussion:

- CAUTION: Federal (U.S.A.) law restricts Advantage Multi® for Dogs to use by or on the order of a licensed veterinarian.
Proactive Heartworm Prevention

Discussion:

• Evidence now exists to support a single topical application of Advantage Multi™ is sufficient to protect a dog against incoming L3 heartworm for at least 28 days (a “month”) after applied
• Once a dog begins monthly administration of Advantage Multi™ it is well protected against heartworms throughout the month, and as more doses are given, the protection is probably even greater

CAUTION: The safety of Advantage Multi® for Dogs has not been established in breeding, pregnant, or lactating dogs.

CAUTION: Federal (U.S.A.) law restricts Advantage Multi® for Dogs to use by or on the order of a licensed veterinarian.

FELINE HEARTWORM DISEASE

Cats are NOT small dogs!
Heartworm Host Differences

Cats are a susceptible but resistant host
– As a resistant host
  • Cats have a much more violent immunologic reaction to HWs than dogs
  • When naturally infected, a much smaller percentage of cats develop adult heartworms than dogs
  • Average adult worm burden is only 1 – 3 worms
Heartworm Host Differences

Cats are a susceptible but resistant host
- As a resistant host
  - Aberrant migration is more common than in dogs (larval migrans)
  - Feline response to heartworm is variable, but 1 worm can cause peracute death in cats
  - In cats, heartworm disease is a lung disease

American Heartworm Society Website: www.heartwormsociety.org/felineheartworminfo.htm

Feline Heartworm Prevalence

- Newest data indicates that in heartworm endemic areas, risk of infection in dogs and cats is equal
  - In some areas, 10 – 14% of shelter cats were heartworm Ab+
- Heavily endemic areas = higher risk

American Heartworm Society Website: www.heartwormsociety.org/felineheartworminfo.htm
Feline Heartworm Prevalence

- Require a canine reservoir (coyote, dog)
- Species of mosquito and environmental conditions impact risk factors
  - Mosquito flight capacity, cold tolerance, preferred habitat, host preference
    - Culex mosquito lives indoors and outdoors, indiscriminant feeder
  - Proximity to competent reservoir

Feline Heartworm Prevention

Why would an indoor cat need chemoprophylaxis?
- In one retrospective study, approximately 25% percent of cats diagnosed with adult heartworms were considered indoor cats
- HW+ incidence rates of indoor and outdoor cats are the same
**Canine vs Feline Heartworm**  
**What We Know**

**Canine**
- Highly susceptible to infection
- Many worms
- Disease depends on dog size, # of worms, exercise
- Worms long lived
- Usually microfilaricmic
- Heart and lungs affected
- Generally easily diagnosed
- Treatment available
- Preventatives available

**Feline**
- Less susceptible to infection
- Few worms
- One worm can cause significant disease
- Worms relatively short lived
- Usually microfilaricmic
- Lungs most often affected
- Diagnosis difficult—usually requires multiple tests
- Only symptomatic treatment available
- Preventatives available

Blagburn B.L., Veterinary Medicine, Sept., 2000

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**Feline Heartworm Timeline**

- Infection with L3 molt to L4 within 3 days
- 45 days – Ab production in the cat begins
- 90 days – Immature adults arrive in pulmonary vasculature
  - Many of these immature adults are eliminated by the cat, but pulmonary pathology results
  - Worms not eliminated by the cat can elicit asthma-like signs
    - dyspnea, cough, pulmonary edema
  - Some cats remain asymptomatic
  - Sudden death can occur (rare)

American Heartworm Society Website. www.heartwormsociety.org/felineheartworminfo.htm

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Feline Heartworm Timeline

• **180 days** – Mature Adults
  – (Ag +)
  – Pulmonary thromboembolism
  – (microfilaria)
  – Dyspnea, cough, vomiting, neuro-signs
  – Pulmonary signs *may* resolve and cat becomes asymptomatic
    • Inhibition of PIM function by adult HW

• **2 – 4 Years** – Death of Adult Heartworms
  – Pulmonary thromboembolism
  – Severe inflammation/Anaphylaxis
  – Sudden death (1 in 5)

Feline Heartworm Pathology

- Pulmonary Intravascular Macrophage
- Unique to cats
- Specialized cells in the capillary beds of the lung in cats
- Envelop and digest foreign material
- PIM response to heartworms causes an acute, intense inflammatory response

Images courtesy of Dr. Clarke Atkins, North Carolina State University
Feline Heartworm Pathology

Phase I
- Coincides with arrival of immature adults to the lungs
- Acute vascular (villous endarteritis) and PIM inflammatory response (immunologic)
- Significant pulmonary pathology
  - Smooth muscle proliferation
  - Inflammation
  - Bronchoconstriction
- Continues even after the death of the immature adult heartworm (up to 18 months)

Phase II
- Death of adult worms
  - Most common time for sudden death
  - 4/5 cats survive this phase

What is HARD?
- Arrival of immature worms in the pulmonary arteries 3 to 4 months post-infection
- Acute vascular and parenchymal inflammatory response to the newly arriving worms
- Initial phase often misdiagnosed as asthma (allergic bronchitis)
- Known as Heartworm Associated Respiratory Disease

2007 Guidelines for the Diagnosis, Prevention and Management of Heartworm (Dirofilaria immitis) Infection in Cats
Clinical Syndromes

- Asymptomatic
- Peracute – adult HW death, immature adult emergence, embolization, aberrant migration
- Acute – immature adult emergence, adult HW death
- Chronic – between immature adult emergence and adult HW death (2 – 4 years)
- Signs often precede Ag+
Feline HARD Clinical Signs

Acute
- Collapse
- Dyspnea
- Convulsions
- Diarrhea/vomiting
- Blindness
- Tachycardia
- Syncope
- Sudden Death

Chronic
- Coughing
- Dyspnea
- Vomiting*
- Lethargy
- Anorexia
- Weight loss
- Chylothorax

*Vomiting unrelated to eating is often seen

Feline Heartworm Signs

Clinical signs in cases of naturally acquired heartworm infection
- 48% dyspnea
- 38% cough
- 28% asymptomatic
  - Incidental finding with signs not heartworm related
- 16% frequent vomiting
- 14% neurologic
- 10% sudden death

2014 AHS Guidelines for the Diagnosis, Prevention and Management of Heartworm (Dirofilaria immitis) Infection in Cats

Feline Heartworm Diagnostics
### Feline Heartworm Diagnostics

Why is heartworm under diagnosed in cats?
- Clinical signs often non-specific
- Usually microfilaremic
- Serologic tests lack specificity/sensitivity for low worm burden
  - Worm burdens are usually small
  - Interpretation of results is challenging
- Aberrant (ectopic) sites more common
- Relatively low incidence/Not looking for it

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### Feline Heartworm Diagnostics

- Physical Exam – usually unrewarding and non-specific
- Cardiac signs – usually not present
- Increased lung sounds occasionally
- Occasionally eosinophilia, rarely microfilaria
- Very Similar to Feline Asthma!
  - Speculation that feline heartworm disease may even be a cause of feline asthma because of intense immunologic reaction to heartworms in cats
  - In endemic areas, heartworm disease should be on the differential in any coughing, dyspneic cat!
Feline Heartworm Diagnostics

Image courtesy of Dr. Clarke Atkins, North Carolina State University

Antigen test
- Detects HW antigens produced in the reproductive tract of sexually mature (adult) female HW – males undetectable
- In cats, 1/3 of adult HW infections consist of only male worms
- If worm burden is less than 3 adult female HW, test sensitivity drops significantly
- Worm burden in cats is generally very low
- 30 – 40% accuracy

2015 CAPC Guidelines for the Diagnosis, Prevention and Management of Heartworm (Dirofilaria immitis) Infection in Cats
Feline HW Diagnostics

Antigen test
- Antigen-antibody complexes occur regularly in cats with adult HW infections – especially in early stages of infection
- Antigen binding renders a false negative test
- Heat treatment of serum samples prior to testing destroys these complexes
- Consider heat treatment in suspicious cases with negative HW antigen test

Bottom line
- Positive HW antigen test confirms adult HW infection
- Negative HW antigen test does not rule out HW infection

Antibody test
- Detects antibodies formed by the cat in response to developmental and adult antigens present on heartworms
- Each test detects a proprietary antibody
- Heartworm antigens vary during different stages of larval development resulting in changes in the type of feline antibody produced
  - Example
    - On day 90, a cat may be Ab (+) with test 'A' and Ab (-) with test 'B'
    - On day 130, the same cat could be Ab (-) with test 'A' and Ab (+) with test 'B'
Feline HW Diagnostics

Antibody test

- Approximately 15 – 25% of cats with adult HW infection are antibody negative
- 80 – 90% of antibody positive cats do not harbor adult HWs
- Up to 30% of cats on HW preventives that are exposed to HWs will convert to antibody positive without developing mature infection or HW related disease

Bottom line
- Positive antibody test
  - May or may not support HWs as a cause of respiratory signs or lesions
  - Proves exposure to L4 HWs
- Negative antibody test
  - Does not rule out current or previous infection
  - May decrease level of suspicion
Feline Heartworm Disease Prevention

• Does prevalence warrant it?
  – FeLV & FIV incidence
• Does disease severity warrant it?
• Is there a good therapy?
• Are there good preventives?

Heartworms in cats are
– Highly pathogenic
– Potentially fatal
– Difficult to diagnose
– Difficult to treat
– So...
WE HAD BETTER PREVENT IT!

Dr. John McCall
University of Georgia

FELINE PROACTIVE HEARTWORM PREVENTION* STUDY
20 cats were divided into 2 groups, 9 non-treated controls and 10 treated cats.

Both Groups
25 O-1 worms/1 day weekly

PRECAUTIONS: Avoid oral ingestion. Children should not come into contact with the application site for 30 minutes following application.
### STUDY RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Mult® Treated Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cats infected</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>No. of cats with adult worms</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>No. of antibody positive cats</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>No. of antigen positive cats</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>No. of cats with pulmonary histopathologic lesions related to D. immitis</td>
<td>0</td>
<td>All antibody positive cats</td>
</tr>
<tr>
<td>% Efficacy</td>
<td>100%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CAUTION: Federal (U.S.A.) law restricts Advantage Mult® to use by or on the order of a licensed veterinarian.

![Normal feline lung](image)

- Alveolar wall
- Alveolar space
Conclusion

This data demonstrates that once steady state is reached, after four consecutive monthly applications...

- Advantage Multi® for Cats (imidacloprid + moxidectin) kills heartworm larvae all month long.†1,2

WARNING: Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight.

DOXYCYCLINE VS. MINOCYCLINE
Doxycycline vs. Minocycline: What's Similar, What's Different, What's New?
M. G. Papich, DVM, MS, DACVCP
North Carolina State University College of Veterinary Medicine
Raleigh, North Carolina

Doxycycline vs. Minocycline
Background:
The use of doxycycline is recommended as adjunctive therapy in adulticidal heartworm treatment to reduce the numbers of the endosymbiont, Wolbachia
  - Wolbachia species are found in many filarial nematodes
  - The systemic release of Wolbachia associated with the death of adult heartworms results in a pro-inflammatory host reaction
  - Doxycycline + macrocyclic lactone treatment prior to melarsomine therapy reduces arterial lesions and thrombi
  - The combination of doxycycline and macrocyclic lactones decreases host immune tolerance to heartworms
  - Doxycycline treatment 'sterilizes' adult heartworms
  - Doxycycline treatment reduces the volume of female heartworms
  - Empirical dose: 10mg/kg BID X 30 days

Doxycycline vs. Minocycline
Background:
Due to lack of availability and cost associated with doxycycline, minocycline has been considered as a substitute
  - The activity of minocycline against the Wolbachia species associated with heartworm disease has not been studied
  - However, minocycline activity has been studied vs. Wolbachia in the filarial worm Onchocerca gutturosa
  - In this study, minocycline out-performed doxycycline
  - Authors propose that the O. gutturosa screen is valid for the screening of antibiotics for anti-Wolbachia activity in other filarids
Minocycline is well absorbed orally
- Minocycline is less protein bound than doxycycline
  - May increase distribution and activity
- Minocycline may have fewer resistance issues
- Minocycline is cleared faster than doxycycline
  - Less tissue exposure
- Approximately twice as lipophilic as doxycycline
  - May result in better intracellular penetration

Doxycycline vs. Minocycline
Pharmacokinetic Information:
- Minocycline is probably a viable alternative to doxycycline and may even be more effective vs. Wolbachia
  - 5 mg/kg BID (fasting)
    - Administer 2 hours post-feeding and 30 minutes prior to feeding

Conclusion:
Theoretically...based upon available studies and new pharmacokinetic information in dogs and cats, it appears that minocycline is probably a viable alternative to doxycycline and may even be more effective vs. Wolbachia

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