HEARTWORM HOTLINE

A Selective Summary of the 2019 Triennial Heartworm Symposium

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The **Heartworm Hotline** column is presented in partnership between ***Today's Veterinary Practice*** and the **American Heartworm Society** (heartwormsociety.org). The goal of the column is to communicate practical and timely information on prevention, diagnosis, and treatment of heartworm disease, as well as highlight current topics related to heartworm research and findings in veterinary medicine.

Heartworm disease prevalence, pathology, and management protocols headlined the 16th American Heartworm Society (AHS) Triennial Symposium, held September 8-11, 2019, in New Orleans. Given the challenges heartworm disease continues to present to the veterinary profession, discovering new strategies for prevention, diagnosis, and treatment is vital to reducing its impact.

An unprecedented 62 speakers and poster presenters were featured in the symposium, focusing on topics that included:

- Heartworm vectors and transmission
- Heartworm prevention
- Heartworm pathology
- Heartworm diagnosis
- *Wolbachia* and heartworm treatment protocols

Following are brief, question-and-answer summaries of presentations on these topics at the 2019 symposium.

These abstracts were published in the proceedings of the 16th Triennial Symposium: Understanding Heartworm Disease: From Science to Solutions, available to American Heartworm Society members at heartwormsociety.org/proceedings-archive. Several abstracts have been published (see Published Abstracts). Many of these abstracts will appear in an upcoming special edition of *Parasites and Vectors*.

HEARTWORM VECTORS AND TRANSMISSION

Q: How is new information about the mosquitoes that transmit heartworms—and about the environment in which mosquitoes live—enhancing our understanding of heartworm prevention?

A: From flooding to urbanization to climate change, many factors affect the likelihood that mosquitoes in a given area will thrive and actively transmit heartworms. Speakers on the topic of vectors and heartworm transmission included Drs. Clarke Atkins, Stephen Jones, Tanja McKay, Doyeon Park, Michael

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Povelones, Marie Varloud, and Sarah Zohdy. Their presentations focused on environmental changes that help foster mosquito proliferation, cell signaling pathways that modulate larval maturation and transmission efficacy in the mosquito, and other vector factors that influence transmission.

Q: Can extreme weather have exponential effects on heartworm prevalence?
A: While the rate of heartworm infection can rise and fall over time in any given area, extreme weather events—especially hurricanes and flooding—can trigger heartworm epidemics. Severe storms result in loss of mosquito abatement practices and increases in standing water, and the resulting mosquito bloom, combined with increased numbers of dogs that are unprotected from heartworm infection due to abandonment and economic disruption, creates a "perfect storm" of conditions for heartworm transmission in the months and years that follow.

Q: Due to the presence of microclimates, is heartworm "season" a misnomer?
A: Environmental microclimates provide warmth and/or moisture that can provide favorable conditions for mosquito activity beyond what might be perceived as the time or place for heartworm transmission. Door entryways, sheds, roof soffits, automobiles, and other protected areas provide focal areas of warmth even as temperatures drop below freezing; meanwhile, golf course ponds, bird baths, and agricultural irrigation can serve as breeding grounds for mosquitoes that transmit heartworms in arid areas.

Q: Can studying mosquito behavior provide insights for future heartworm prevention strategies?
A: Not only are multiple species of mosquitoes known to transmit heartworms, but different species feed at different times of the day and in different locations. A study conducted by researchers at the University of Arkansas found a prevalence of *Dirofilaria immitis* infection from 5.9% to 12.5% in daytime-feeding mosquitoes congregating near door entryways at 4 residential locations. Meanwhile, studies at Auburn University determined that (1) the wingbeat frequency of mosquitoes infected with L3 (infective stage) *D. immitis* larvae slows significantly (a factor that may aid identification of infected mosquitoes) and (2) volatile organic compounds and phenols in the breath of heartworm-infected dogs may serve as mosquito attractants, while the breath of non-infected dogs contains alkane hydrocarbons that are known mosquito repellents.

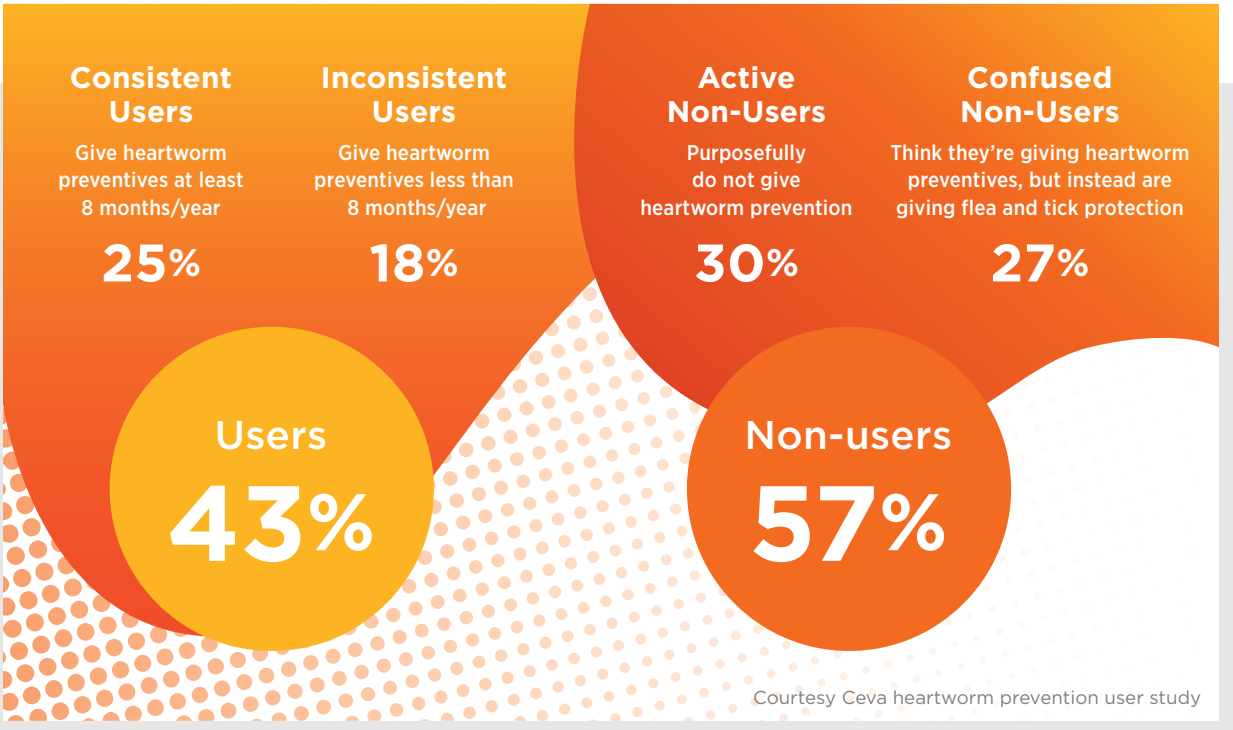

FIGURE 1. Heartworm Preventive Users vs. Non-users

More From the 16th Triennial Heartworm Symposium

The 16th Triennial American Heartworm Society Symposium was attended by scientists and clinicians from 13 countries and 35 states. A total of 62 speakers and poster presenters shared their findings during the 3½-day symposium. To see a snapshot, visit bit.ly/2U4dSNr.

In addition, the AHS website and YouTube page features videos of interviews with a number of symposium speakers and moderators, including Drs. Marisa Ames, Clarke Atkins, Doug Carithers, Mark Cousins, Deb Horwitz, Stephen Jones, Molly Savadelis, and Lindsay Starkey. These videos can be viewed at youtube.com/user/americanheartworm.

Scientific papers from the symposium will be published in a future issue of *Veterinary Parasitology*. Members of the AHS can access all past symposium proceedings free of charge. To join the AHS, visit heartwormsociety.org/membership/join.

HEARTWORM PREVENTION

Q: What are the barriers to client compliance?

A: Studies and practitioner testimony confirm that there is no substitute for taking the time to educate dog and cat owners about the importance of heartworm prevention. Speakers on heartworm prevention and compliance included Drs. Mark Cousins, Stephen Jones, Thomas Nelson, and Edward Wakem, with presentations and panel discussions addressing the real-world obstacles to heartworm prevention and strategies to overcome them.

Q: Is there a link between owner education and consistent heartworm preventive usage?

A: In a survey conducted by Ceva Animal Health of 565 dog owners, less than half (43%) used heartworm preventives at all, while just 25% of all owners gave preventives consistently (e.g., at least 8 months a year). Roughly half of the 57% that gave no preventives at all did so purposefully, while the other half mistook their flea/tick preventive for heartworm preventives (FIGURE 1). Meanwhile, a strong correlation was noted between consistent use of preventives and understanding of how heartworm preventives work. Barriers to consistent usage included prescription requirement, cost, belief the dog was not at risk, no strong veterinarian recommendations, and forgetfulness.

Q: Failure of veterinarians to recommend feline heartworm prevention may be linked to diagnosis difficulties and the inherent difference between canine and feline heartworm disease. Can you explain?

A: With a dearth of controlled studies being conducted on feline heartworm disease, recommending prevention is a practice frequently overlooked by veterinarians. Meanwhile, the tendency of cats to abort *D. immitis* infections in the immature stage (which can still cause a heartworm-associated respiratory disease, or HARD), along with smaller numbers of heartworms overall and more male-only infections, has reinforced the belief among many practitioners that heartworm incidence in cats is low and prevention is a low priority. Rather than relying solely on results of heartworm antigen tests to determine if preventives are needed in a given feline patient, veterinarians were advised to consider the relatively high incidence of HARD in cats and the lack of approved adulticide treatments to justify the investment in disease prevention.

HEARTWORM PATHOLOGY

Q: How do heartworms affect their host(s)?

A: Heartworm disease is far more than a disease of the heart, lungs, and arteries. Studies show that heartworm infection can lead to multisystemic effects in both dogs and cats. Presenters on this topic included Drs. Rick Alleman, Elena Carretón, Rodrigo Morchón Garcia, Stephen Jones, Imke Maerz, and Kaori Sakamoto, and topics included clinical pathologic changes in animals with heartworm disease as well as testing methods used to evaluate where, when, and how damage from the disease is occurring.

Q: Can heartworms and circulating microfilariae cause widespread organ damage?

A: Heartworms and microfilariae live within the host's vascular system, with microfilariae circulating to tissues and causing structural damage to organs such as the kidneys and lungs. In addition, soluble antigens released by heartworms form immune complexes that damage tissues, causing variability in disease manifestations and therapy-associated adverse effects.

Q: Certain assays conducted on heartworm-positive animals may help guide medical management of these patients prior to starting adulticide therapy. How?

A: These include complete blood count and biochemical profile and quantification of proteinuria via the urine protein-to-creatinine ratio, as well as

thoracic radiographs and echocardiography to detect the cardiovascular, pulmonary, and systemic impacts of heartworm disease. Additional biomarkers may also be useful. A study on renal damage from heartworm infection indicated that symmetric dimethylarginine (SDMA) may facilitate early detection of renal damage in dogs without other markers such as proteinuria.

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HEARTWORM DIAGNOSIS

Q: What's new in heartworm diagnosis? How are heartworm researchers refining testing techniques?
A: While heartworm antigen tests are easy to use and reliable in a majority of cases, the conundrum of immune complexes—as well as how best to unmask them—highlighted the need for veterinarians to conduct follow-up testing when their clinical judgment warrants it, while making informed choices about the antigen and microfilaria tests they use. Presenters on this topic included Drs. Clarke Atkins, Cassan Pulaski, Lindsay Starkey, and Guilherme Verocai, as well as Jeff Gruntmeir.

Q: Are heartworm antigen tests interchangeable?
A: A comparative evaluation of 2 in-clinic antigen assays was conducted with field samples from Tennessee, Louisiana, and Texas to compare the specificity and sensitivity of the IDEXX 4Dx Plus and Zoetis FLEX4 heartworm antigen tests. While specificity was high for both tests in the study, the 4Dx Plus test was significantly more sensitive than the FLEX4 test (97.4% vs. 76.9% sensitivity, respectively) in detecting heartworm antigen.

Q: How can microfilaria testing be made easier?
A: Mobile phone-based technology may someday make it possible to quantify microfilaria in whole blood loaded on a disposable glass capillary. Not only could this technology provide a quick and cost-effective strategy for point-of-care diagnosis but could also be used to monitor microfilaria suppression in suspected cases of heartworm resistance.

Q: Testing accuracy is enhanced by heat and acid treatment. Can you explain?
A: In cases of "no antigen detected" test results, both heat treatment and acid treatment dissociate immune complexes and improve test sensitivity. Although available antigen tests are very sensitive, all-male infections are often negative (i.e., no antigen detected). In a Florida study of sheltered dogs whose heartworm infection was determined by necropsy to consist of only males, heat treatment of serum improved detection of antigen. A separate study at Auburn University showed that acid treatment had a similar efficacy as heat treatment in unmasking immune complexes. Acid treatment had an added advantage of requiring a much smaller serum sample than heat treatment (see TABLE 1). Although neither heat nor acid treatment of plasma in the Auburn study caused a false-positive antigen test result, the incidence of false-positive tests after heat or acid treatment in naturally infected dogs remains to be determined.

WOLBACHIA AND HEARTWORM TREATMENT PROTOCOLS

Q: Can heartworm treatment be faster, cheaper, and/or easier?

TABLE 1 Methodology for Heat vs. Acid Treatment of Serum Samples

METHOD	ADDITIONAL REAGENTS OR EQUIPMENT	MICROCENTRIFUGE REQUIRED?	STARTING VOLUME NEEDED FOR: 150 µL (TRIPLICATE)	50 µL (1 TEST)	PREP TIME
Normal	N/A	No	150 µL	50 µL	N/A
Acid treatment	7.5% TCA 1M Trizma Micro-pipettor	Yes	100–200 µL	50 µL	~30 min
Heat treatment	Heat-block	Yes	1000–1500+ µL	500+ µL	~22 min

TCA=trichloroacetic acid

A: Treatment of adult heartworm infections in dogs, while effective, is not without its challenges. Avoiding treatment complications, minimizing adverse events, and making treatment affordable for owners are common goals for both practitioners and pet owners. Speakers on heartworm treatment included Drs. Marisa Ames, Elena Carretón, Deb Horwitz, and Molly Savadelis.

Q: Should we be making changes to current protocols?

A: Alternatives to current protocols for heartworm treatment are continually being evaluated, due to the real-world challenges of sourcing cost-effective medications and following protocols that require months of treatment and multiple veterinary visits. Reducing *Wolbachia* numbers is a cornerstone of effective heartworm treatment, but doxycycline—the antibiotic recommended in the AHS pre-treatment protocol—is expensive and can sometimes be difficult to source. Researchers from the Liverpool School of Tropical Medicine described ongoing endeavors in the search for novel anti-*Wolbachia* compounds. A study comparing doxycycline with minocycline revealed that minocycline is less effective than doxycycline at eliminating *Wolbachia*, and gastrointestinal side effects were seen with similar frequency in both the minocycline and doxycycline 10 mg/kg q12h treatment groups.[1] Meanwhile, a study in which the pre-treatment period was shortened from 60 days to 30 days (i.e., macrocyclic lactone preventive and doxycycline initiated at diagnosis and first injection of melarsomine given at day 30 instead of day 60) indicated that the abbreviated protocol may present a potentially valid alternative.[2]

TABLE 2 Treatment of Severe Heartworm Disease

CONDITION	TIME OF ONSET	COMMENTS	TREATMENT
Pneumonitis *Signs:* Cough, tachypnea, dyspnea	Timing varies; associated with death of mf or presence/death of adult worms	Radiographs: perivascular inlammatory interstitial infiltrates (Note: This is not cardiogenic edema, and furosemide is not indicated)	▪ Oxygen ▪ Dexamethasone (0.2 mg/kg IV ▪ Home therapy: prednisolone 0.5 mg/kg PO q12h to q24h; taper to the lowest dose needed to control cough
HW-induced PTE *Signs:* Tachypnea, dyspnea, cyanosis, collapse, cough	5–IO days (range, 3–21 days) after melarsomine administration; also may occur spontaneously during HWD	Inevitable, but severity varies markedly; risk of severe HW-induced PTE with exercise or rapid worm kill (2-dose melarsomine protocol)	▪ Oxygen ▪ Sildenafil (1–2 mg/kg PO q8h ▪ Corticosteroid therapy, route, and agent determined by severity and patient's need for rapid treatment If no contraindication; anticoagulant therapy may be beneficial: clopidogrel (1–2 mg/kg PO q24h)
Nonarsenical PTE *Signs:* Same as above	Weeks to months after initiation of nonarsenical adulticide protocol	Exercise restriction should be imposed for months when using a nonarsenical protocol	Same as above
Right-sided CHF *Signs:* Abdominal distention, tachypnea, dyspnea, jugular distention, cachexia	Usually associated with chronic, untreated HWD	Recommend stabilization for weeks to months, with severe exercise restriction prior to adulticide administration	▪ Furosemide ("at home" dose typically 2–6 mg/kg/d PO) Pimobendan (0.25 mg/kg PO q12h) ▪ Sildenafil (1–2 mg/kg PO q8h) Spironolactone (2 mg/kg PO q24h) ▪ Centesis
Caval syndrome *Signs:* Low output and right-sided CHF, pallor, murmur, pigmenturia, collapse	Usually associated with chronic, untreated HWD	Stabilization may include fluid resuscitation, vasopressors, and blood products to normalize coagulopathy; prompt HW removal	Heavy sedation or general anesthesia, jugular venotomy, and worm extraction with forceps,[a] gooseneck snare,[b] or endovascular snare.[c] Procedure is followed by stabilization for weeks to months, with severe exercise restriction prior to adulticide administration.

CHF=congestive heart failure; HW=heartworm(s); HWD=heartworm disease; PTE=pulmonary thromboembolism; mf=microfilariae; ML=macrocyclic lactone
[a]ClearIt® Heartworm Removal Device (Avalon Medical, avalonmed.com)
[b]Amplatz Gooseneck® Snare Kit (Medtronic, medtronic.com)
[c]ENSnare® (Merit Medical Systems, merit.com)

Q: What about patients with severe heartworm disease?

A: While most dogs with heartworm infections have either no clinical signs or mild signs, a small percentage of dogs will develop severe clinical signs arising from pneumonitis, pulmonary hypertension, right-sided heart failure, and caval syndrome. The likelihood of complications associated with heartworm disease increases with the chronicity of infection. Prognosis is dependent on stabilization, the ability to administer subsequent adulticide therapy, and the ability of the family to commit to treatment of chronic conditions (see **TABLE 2**).

Q: How can we overcome the challenges associated with the "cage rest" recommendation?

A: One of the practical challenges associated with heartworm treatment is keeping dogs quiet during heartworm treatment to avoid complications associated with worm death. Imposing the no-exercise mandate on owners and dogs can meet with better acceptance if positioned as "rest time for recovery." Meanwhile, finding creative ways to quietly engage with dogs in treatment can help provide enrichment and avert erosion of the owner's bond with the pet. **TVP**

References

1. Savadelis MD, Day KM, Bradner JL, et al. Efficacy and side effects of doxycycline versus minocycline in the three-dose melarsomine canine adulticidal heartworm treatment protocol. *Parasit Vectors* 2018;11(1):671.
2. Carretón E, Falcón-Cordón Y, Falcón-Cordón S, et al. Variation of the adulticide protocol for the treatment of canine heartworm infection: Can it be shorter? *Vet Parasitol* 2019;271:54-56.

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