



BRINGING THE 15TH TRIENNIAL HEARTWORM SYMPOSIUM TO YOU

Foreword

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Every three years, hundreds of heartworm researchers, veterinarians and students mark their calendars for the Triennial Heartworm Symposium, a scientific meeting that convenes the world's leading experts on heartworm disease in sharing the latest information and research. This symposium is one of the most important functions in the charter of the American Heartworm Society (AHS) as we fulfill our mission of leading the veterinary profession and the pet-owning public in the understanding of heartworm disease.

The 2016 symposium, which was held September 11-13, 2016, in New Orleans, covered a variety of topics, from the pros and cons of different heartworm treatment protocols to the latest insights on mosquito vectors and blocking strategies to updates on heartworm resistance and diagnostic techniques. The presentations and panel discussions confirmed the complexity of understanding, preventing and treating heartworm disease, and affirmed why its persistence continues to confound those of us who work to prevent, diagnose and treat it every day.

The 2016 Triennial Heartworm Symposium included more than 50 presentations, panel discussions and posters. While it's not possible to share all of the information from the Triennial Symposium in just a few short pages, we wanted to bring you some of the key findings. In this *Clinician's Brief* supplement, we've posed a series of questions to a group of speakers and moderators who took the stage at the symposium. We hope the answers will prove interesting and of value to you in your daily practice.

OUR EXPERTS

Clarke Atkins, DVM, DACVIM
Professor Emeritus, Medicine and Cardiology
North Carolina State University

Byron Blagburn, PhD
Distinguished University Professor
Auburn University

Ray Kaplan, DVM, PhD
Professor, Department of Infectious Diseases
University of Georgia

Laura Kramer, DVM, PhD, DEVPC
Associate Professor of Veterinary Parasitology
University of Parma Veterinary School

Tanja McKay, PhD
Professor of Entomology
Arkansas State University

Matthew Miller, DVM, DACVIM
Veterinary Cardiologist, VETMED
Phoenix, Arizona

The Q&A that follows reflects the opinions of some of the leading experts on heartworm disease and is not intended as an official statement from the American Heartworm Society. For more information from the 2016 symposium, please visit our website at heartwormsociety.org.

HEARTWORM DISEASE AND ITS SPREAD

Q. What are we learning about the spread of heartworm disease?



DR. LAURA KRAMER: Globally, the areas in which heartworm disease has become endemic are growing. I conduct my research in Europe, and over

the past 10 years there, the disease has spread from the southern areas, including Italy, to central and eastern Europe. This was actually predicted by my University of Parma colleague Dr. Claudio Genchi, whose forecast model used meteorological data to predict where heartworm disease could be transmitted in the future.

We definitely see parallels to this in what is happening in the United States. We know that climate change also is a factor here, and that infected dogs are moving around much more than they did in the past. We also know that we have new competent mosquito vectors that can transmit the disease. As a result, we've seen movement in the United States of heartworm infection from the South and Southeast towards the western and northern states.

The bottom line: veterinarians everywhere need to be aware of the spread of heartworm disease—and that the introduction of infected dogs into a previously “non-endemic” area can present a new health risk to their patients.

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– Dr. Tanja McKay

Q. What do we know about the mosquito vectors that spread heartworms?



DR. TANJA MCKAY: A variety of mosquito species live in the United States, with 10 to 12 believed to be the major players in heartworm

transmission. Each species has a different habitat, emerging from ditches, ponds or even small containers of water. Different species also have different travel patterns. Some stay near their emergence site, while others can travel as far as two miles. Some prefer the outdoors, while other mosquitoes congregate around doorways and windows in order to come inside to feed on people and pets. Understanding these interactions and ecological habits is important to understanding the transmission of heartworm.

Different species also may be active and feeding at different times of the day. Some mosquito species, such as *Aedes albopictus* and *Aedes aegypti* (both of which are associated with spreading the Zika virus, as well as heartworm), prefer feeding during daylight hours. Other species may be dusk or evening feeders. Knowing which mosquito species are prevalent in an area, as well as when they are active, allows the veterinarian to more accurately predict when mosquitoes in a specific locale can transmit heartworm.

Keep in mind, though, that the situation is always dynamic; the distribution of *A. albopictus* and *A. aegypti* mosquitoes, for example, was different 20 years ago than it is today. Weather patterns change and we have a mobile society, which can cause vectors and the diseases they can carry to change in a relatively short period of time.

Q. Knowing how rapidly vectors and diseases can spread to new, previously uninfected areas, what can we learn from studies on human mosquito-borne disease?



DR. CLARKE ATKINS: We heard a very interesting presentation at the symposium from Dr. Audrey Odom, a pediatrician who is studying the use of

breath-based diagnostics for early detection of malaria. She has learned that the *Anopheles* mosquito that transmits the protozoan parasite *Plasmodium falciparum*, is more likely to feed on malaria-infected individuals because they secrete volatile organic compounds that are known mosquito attractants. If a similar pattern were to be confirmed in animals infected with *Dirofilaria immitis*, this discovery might hold promise in the future for both heartworm diagnosis and intervention.

MULTI-MODAL HEARTWORM PREVENTION

Q. On a related topic, one of the heartworm prevention strategies discussed at the Triennial Symposium was “multimodal” prevention, which includes incorporating strategies to address the mosquito vector in preventing heartworm transmission. Can you explain?



DR. MATTHEW MILLER: Historically we have emphasized the use of macrocyclic lactone (ML) containing products in the prevention of heartworm

infections. If we think about standard ML therapy, we are basically accepting the fact that transmission will occur, but we are going to prevent maturation of the infection. Multimodal therapy includes the use of a combination repellent/insecticide to help prevent that initial

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– Dr. Matthew Miller

infection. At the same time, we want to make sure we have a back-up plan. Knowing that the repellent will not be 100% effective, we have an ML onboard year-round to make sure that if transmission occurs, the infection never becomes an adult heartworm infection.

Q. What are the limitations of insecticide/repellent-only therapy?

DR. MILLER: No one is recommending that mosquito-blocking therapy be used in exchange for a macrocyclic lactone (ML). It’s an add-on, and the primary means of prevention needs to be an ML. What we’re trying to do with this approach is minimize the number of bites that occur. If we simultaneously administer an ML year-round to prevent maturation of infections, that combination therapy may optimize the likelihood that we prevent transmission. In addition, if we have a dog that’s already infected and is microfilaremic, we can reduce the likelihood that a mosquito will bite that dog and serve as a vector to another patient close by.



HEARTWORM DIAGNOSTICS

Q. A significant amount of discussion was focused during the Triennial Symposium on the subject of heat treating blood samples to reverse false-negative results. How would you summarize the findings?



DR. BYRON BLAGBURN: The concept of disassociating antigens and antibodies has been around for 2-3 decades. At one time, heartworm tests

used by veterinarians had a mandated step that was either acid- or enzyme-based in which you disassociated antibodies. However, that step was considered by some veterinarians to be too complicated, so the manufacturers eliminated it in their patient-side tests. Today our research is addressing it again because we know that some antigen blocking does occur. We don't know if it's the inflammation caused by heartworm or another agent—or the existence of antibodies in excessive amounts in individual pets—but we know that it occurs. And we know that by using heat, which is the topic that's most popular now, we can disassociate those antibodies and convert those negatives to positives.

Q. How should practicing veterinarians interpret this information? Should they alter their diagnostic protocols?

DR. BLAGBURN: I think it's important to note that veterinarians should not feel they need to heat-treat every sample that tests negative. However, if a practitioner suspects heartworm infection—for instance, if they see microfilariae (MF) in conjunction with a negative antigen test, or get a negative antigen test on a dog with clinical signs—those dogs are good candidates for heat treatment of their serum, with retesting for heartworm antigens.

"I think it's important to note that veterinarians should not feel they need to heat-treat every sample that tests negative."

– Dr. Byron Blagburn

Q. What about heat treatment of feline serum? What do we know?

DR. BLAGBURN: Heat treatment of feline serum in many ways may be more interesting, and the result may be more applicable. Because cats have low worm burdens and more male-only infections, they are much more likely to be antigen-negative, even when heartworm-infected. Recent studies show that experimental heartworm infections in cats that test negative on this antigen test can be converted to positive with heat treatment of serum. I think the most important point about reversal with feline heartworm is that when you heat treat antibody-positive serum, you increase the number of antigen positives and there's better correlation between antigen and antibodies.

LACK OF EFFICACY AND RESISTANCE TO HEARTWORM PREVENTIVES

Q. What do we know about heartworm resistance—and what don't we know?

DR. CLARKE ATKINS: Since the first peer-reviewed article on the potential emergence of resistant heartworm isolates to ML preventives was published more than ten years ago, scientists have been working to better understand why cases of heartworm infections have developed in dogs purported to have been treated appropriately with heartworm preventives, as well as increased difficulty in clearing heartworm microfilariae with ML medications. What we do know is that

heartworm resistance violates the classical rules of resistance. These “rules” include:

Resistance is much less likely to occur in a region with large refugia. Suspect ML lack of efficacy (LOE) cases have been reported predominantly in the lower Mississippi Delta region; however, the Delta has the largest refugia for heartworm in the U.S.

Resistance is characterized as rapidly spreading. LOE reports have not occurred in numbers greater than expected outside of the Mississippi Delta.

Resistance is forever. The incidence of LOEs peaked in 2009 and by 2011 had dropped by nearly half. Meanwhile, the vast majority of LOE reports have been invalidated with careful scrutiny of medical records and product purchase history.



“In the vast majority of reported LOE cases, compliance actually is the culprit. Fortunately, we have the ability to affect this.”

– Dr. Clarke Atkins

So we know that resistance is real, and that it has been demonstrated with all four ML molecules in veterinary use. However, we don’t know the geographical extent of heartworm resistance or how much resistance plays a role in treatment failure (LOEs).



Q. What studies are needed to better address heartworm resistance?



DR. RAY KAPLAN: It’s important to study the genetics of drug resistance in heartworm. We want to try to identify which genes are involved, as well

as markers that can be used for diagnosis. Currently we don’t know which genes might be involved or what the inheritance patterns of resistance are. All of these things are going to be very important for developing a diagnostic test and then developing models that will enable us to predict the likelihood of spread. We hope that if we can develop some good diagnostic molecular markers, we can then perform molecular epidemiological studies, taking samples from around the country and looking for the specific alleles that are involved with resistance. That is the goal. There’s a lot of work before we get there.

Q. Not every case of heartworm preventive “failure” is a resistant case. When should veterinarians suspect resistance?

DR. KAPLAN: Many things can cause failure of prevention other than resistance (e.g. poor owner compliance). The problem is that reports are just reports, and there’s no way to prove if they are associated with true resistance or not. The FDA has received more than 45,000 reports from around the country since 2005 and, as yet, most are not validated. Veterinarians need to look at the medical history, the testing history and the purchase history and decide if product failure is likely. If there are gaps in the purchase history, the veterinarian should question the conclusion that it’s resistant.

Q. You and your colleague, Dr. Andy Moorhead, recently developed an algorithm that may help veterinarians know whether to suspect they have a resistant heartworm isolate. Can you explain?

DR. KAPLAN: Currently we have no diagnostic test for resistance, so when a case comes in that looks like it might be resistant, a veterinarian is unable to easily confirm or refute whether resistance is there. To address this problem, Dr. Moorhead and I created a decision tree to help practitioners make the distinction of whether they might have a resistant case.

We recommend performing a microfilarial (MF) suppression test by taking a blood sample and determining the number of microfilariae present using a Knott's test, then treating the dog with a microfilaricidal dose of ivermectin or milbemycin oxime. A week later, we recommend performing another MF count. In most studies, a very rapid and profound reduction in MF numbers was seen. Thus one should expect to see a reduction of greater than 75 percent, and typically 90 percent or higher. So if a practitioner sees less than a 75 percent reduction in MF, the case can be considered highly suspicious for resistance.

Q. What additional advice do you have for veterinarians?

DR. ATKINS: In the vast majority of reported LOE cases, compliance actually is the culprit. Fortunately, we have the ability to affect this. Veterinarians also need to know that MLs



“Veterinarians need to look at the medical history, the testing history and the purchase history and decide if product failure is likely.”


– Dr. Ray Kaplan

should be used year-round, as the American Heartworm Society advocates. I also believe that in areas where exposure potential is massive—where there are lots of mosquitoes and a very high mosquito infectivity rate—it is even more important to make sure that compliance is exact.

HEARTWORM TREATMENT PROTOCOLS

Q. You feel strongly about the importance of *Wolbachia* elimination as part of heartworm treatment. Can you explain?

DR. LAURA KRAMER: I think that the discovery of *Wolbachia* within the heartworm was one of the most important discoveries made within the last 20 years in parasitology, and it has important repercussions in human filarial infections as well.



“If we eliminate *Wolbachia* through doxycycline therapy prior to treatment with melarsomine...we know that lung pathology and clinical manifestations of adulticidal therapy, are much, much lower than if we weren't using doxycycline.”

– Dr. Laura Kramer

What researchers have seen after years of intensive research is that these bacteria are essential for heartworm survival, reproduction and development. We know that they are very strongly pro-inflammatory and that they're one of the most important components in post-adulticide pathology. When a heartworm dies, both the heartworm and the *Wolbachia* release somatic antigens, with the latter being an important contributor to the negative effects of worm death on the host. If we eliminate *Wolbachia* through doxycycline therapy prior

to treatment with melarsomine, or simply administer it with macrocyclic lactones in an adulticidal protocol, we know that lung pathology and clinical manifestations of adulticidal therapy, are much, much lower than if we weren't using doxycycline. It's fundamental to maintaining cardiovascular health during and after adulticidal therapy for heartworm disease.

Q. You and others have been studying adulticide protocols for dirofilarial infections. What is the value of exploring alternative protocols for heartworm treatment?

DR. KRAMER: First of all, it's important to make clear that looking for alternative protocols does not mean that melarsomine isn't the drug of choice for heartworm treatment; it's an excellent drug. At the same time, we know that mild to serious side effects can result with melarsomine, that problems can arise with owner compliance during treatment and, in many parts of the world, there are issues with melarsomine availability and affordability. Identifying alternative adulticidal protocols will help to guarantee that each pet and owner's needs are met.

My group in Parma has conducted field studies that use macrocyclic lactones and antibiotics, particular doxycycline, to eliminate adult parasites. These combinations have been found to be very effective in eliminating adult parasites, although they require time—up to a year or more (hence, heartworm elimination

is slower than with melarsomine). Our most recent studies were with combinations of moxidectin and doxycycline, which were found to have superior efficacy to an ivermectin/doxycycline combination. Our findings can be applied in two ways: (1) we can use a combination of macrocyclic lactones and doxycycline to prep dogs for Immiticide therapy, thereby reducing lung pathology, or (2) if melarsomine therapy is not possible, we can use the combination as an alternative adulticidal treatment.



2016 AHS Triennial Symposium

JOIN THE AHS COMMUNITY

Heartworm disease is one of the most important diseases in companion animals and it's vital that practitioners stay informed of the latest developments. The best way to do so is to join one—or all—of the AHS communities.



Become an AHS member.

Members receive a number of benefits, from discounts on client education materials and the triennial symposium registration, to exclusive materials, such as the AHS symposium proceedings and the quarterly AHS Bulletin. Information on joining is available on heartwormsociety.org/membership/benefits.html



Join the AHS Facebook community.

Our Facebook page connects you to the latest information on heartworm, as well as frequent posts that can be shared with your practice's social communities. You can find us at facebook.com/heartwormsociety.



Follow AHS on Twitter.

Follow us on Twitter at [AHS_Think12](https://twitter.com/AHS_Think12) and link to a wide range of resources and debates. Our Twitter page is also a great place to follow live during AHS symposia.

Both our Facebook and Twitter pages are run by veterinarians who serve on the AHS executive board.



Tune in to AHS on YouTube.

Check out video interviews with speakers from the 2016 Triennial Heartworm Symposium, and download client education videos for use in your practice. We're at youtube.com/user/americanheartworm.

THE AMERICAN HEARTWORM SOCIETY AND YOU

The American Heartworm Society (AHS) is focused on serving the needs of the veterinary profession. Here's how you can take advantage of AHS programs:

HEARTWORM SYMPOSIA

The AHS brings the latest in scientific information to veterinary professionals through scientific symposia. Opportunities include:

- **The Triennial Heartworm Symposium.**

This comprehensive conference takes place every three years, and includes presentations by leading heartworm experts with attendees from all over the United States and the world. The next symposium will be held in 2019.

- **NAVC Heartworm Symposium.**

Every year, AHS sponsors a half-day symposium for attendees of the North American Veterinary Conference in Orlando.

- **Heartworm University.**

This traveling symposium is a half-day or day-long continuing education session offered free of charge to veterinarians and veterinary technicians, and is designed to bring in-depth information on heartworm disease to veterinarians in different locales. Many Heartworm University sessions are held in conjunction with state veterinary medical association meetings.



HEARTWORMSOCIETY.ORG

The American Heartworm Society website is one of the most important resources offered by the AHS. Here, veterinary professionals can access the following:

- **The American Heartworm Society guidelines**, in both comprehensive and summary formats.

- **Heartworm incidence maps**, which are based on a triennial nationwide survey of thousands of veterinary practices.

- **Client education materials**, including brochures, videos, infographics, and other materials on heartworm and pet care. The website also includes a "heartworm basics" section, which includes information and FAQs written specifically for pet owners.

- **Heartworm resources**, including C.E. videos, practice tools, shelter resources, FAQs and much, much more for veterinarians, shelter personnel and pet owners. You can also subscribe to emails that keep you up to date on our latest tools.



The AHS website is also a resource when challenges arise, whether you're looking for information on lack of efficacy, diagnostic techniques, heartworm treatment or other clinical issues. In addition, you can learn more on our website about the AHS mission as well as the AHS' officers and executive board.

