

# DOXYCYCLINE in the Management of HEARTWORM DISEASE

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The *Heartworm Hotline* column is cosponsored by *Today's Veterinary Practice* and *The American Heartworm Society* ([heartwormsociety.org](http://heartwormsociety.org)). Each article presents a question or questions on a particular area related to heartworm infection, prevention, diagnostics, and/or treatment.

You asked...

## What role does doxycycline play in the management of heartworm disease?

The exact role of doxycycline in the management of heartworm disease (HWD) is not well established.

However, virtually all experts in the field would agree that doxycycline has a role in therapy and most U.S. veterinarians incorporate it into their management of HWD (**Figure 1**).

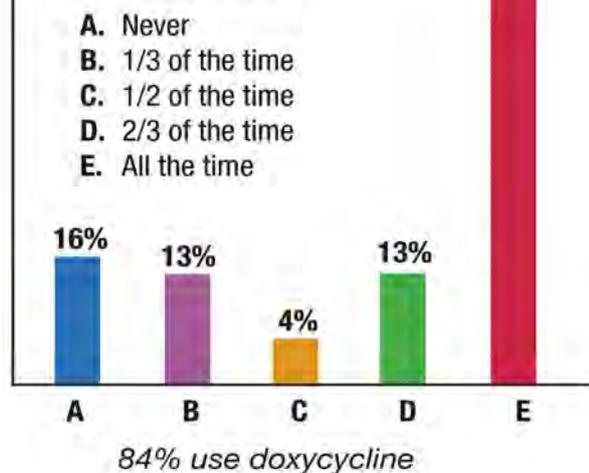
Several important questions regarding doxycycline remain unanswered, including:

- What is the optimum concomitant therapy (ie, most data to date have been generated using concomitant administration of ivermectin)?
- What is the exact dosage, time-point for initiation, and duration of therapy?
- What are the risk and cost to benefit ratios?
- In which specific disease stage(s) is doxycycline useful?

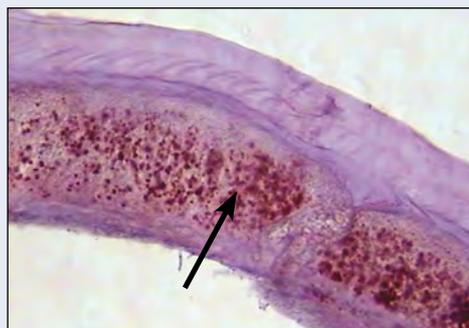
## Doxycycline versus *Wolbachia*

The benefits of doxycycline result from its ability to remove or reduce the burden of *Wolbachia*, a rickettsial organism that exists in a symbiotic relationship with heartworms (and other filarids), occupying the reproductive tract and lateral chords of the host parasite (**Figure 2**).

### In my practice, we use doxycycline as part of adulticide therapy:



**Figure 1.** Graphic representation of doxycycline use by veterinarians attending the American Heartworm Society sessions at the 2012 NAVC Conference; it is apparent that 84% of veterinarians surveyed use doxycycline on occasion (1/3 or more) in the management of HWD.



**Figure 2.** An adult female heartworm is shown with *Wolbachia* antigen evident as stained material (arrow); the endosymbiont inhabits the lateral chord and the uterus. Courtesy Dr. Laura Kramer

### Benefits of Anti-*Wolbachia* Therapy

- Reduces ability of parasite to reproduce
- Reduces infectivity
- Potential adulticidal therapy and/or enhancement of slow- or soft-kill efficacy
- Reduces microfilarial burdens more effectively, safely, and rapidly
- Reduces reaction to worm death, both spontaneous (presumably) and postadulticide
- Kills or impairs developing larvae



*Wolbachia* are necessary for the parasite (in this case, *Dirofilaria immitis*) to develop, thrive, reproduce, and maintain infectivity.

Doxycycline has been used to (presumably) rid the parasite of *Wolbachia* organisms; therefore, *D immitis* organisms do not thrive, may deteriorate and die, and have reduced reproductive potential, which helps manage HWD in infected dogs and reduces potential for infection in other dogs.

Potential and realized benefits derived from anti-*Wolbachia* therapy include:

#### 1. Reduced Ability of Parasite to Reproduce

It has been shown that the *Wolbachia* organism is suppressed (killed) by doxycycline and the resulting, negative effects on the heartworm reproductive system renders the parasite infertile or less fertile (temporarily?), with reduced microfilarial numbers.<sup>1,2,3</sup>

#### 2. Reduced Infectivity

In doxycycline-treated dogs, even if microfilariae are produced and ingested in a mosquito's blood meal, the resultant L3 are incapable of producing infection, reducing the spread of HWD.<sup>1,2,3</sup>

#### 3. Potentiate Adulticidal Therapy and/or Enhancement of Slow- or Soft-kill Efficacy

Most agree that *Wolbachia* is an obligatory symbiont for *D immitis*, which gives hope that *Wolbachia* eradication with antibiotics would result in the nematode's demise. Unfortunately, prolonged doxycycline therapy does not kill heartworms because they are not sufficiently bound to their bacterial symbionts.<sup>4</sup>

Nevertheless, 2 studies<sup>3,5</sup> have demonstrated that doxycycline shortens the time until worm death when administered chronically with ivermectin/pyrantel at preventive dosages, but with a decreased dosing interval.<sup>3,5</sup>

**Study 1:** Using surgically transplanted worms, it was shown that a combination of:

- **Weekly ivermectin** (at the monthly preventive dosage of 6 mcg/kg PO) **and**
- **Daily doxycycline** (10 mg/kg PO Q 24 H for 24 weeks of a 36-week study) reduced heartworm burden by 78% after 9 months of therapy as compared to control dogs.<sup>3</sup>

**Study 2:** Using echocardiography, this study evaluated the effect of:

- **Daily doxycycline** (10 mg/kg PO Q 24 H for 30 days) **and**
- **Ivermectin/pyrantel** (6–14 mcg/kg PO every 15 days for 180 days; then monthly) on microfilaremia, heartworm antigenemia, and parasite load. In naturally-infected dogs from an endemic region of Italy, all dogs became negative for circulating microfilariae by day 90 and 73% became antigen negative by day 300.<sup>5</sup>

The results of these studies suggest that the combination of doxycycline and ivermectin is (slowly) adulticidal in dogs with *D immitis*, which indicates that doxycycline enhances therapy for the soft- or slow-kill method.

#### 4. Effective, Safe, & Rapid Reduction of Microfilarial Burdens

In the transplanted worm model mentioned in Study 1, it was shown that a combination of weekly ivermectin (6 mcg/kg) and daily doxycycline (10 mg/kg Q 24 H) eliminated microfilariae over 8 to 12 weeks.<sup>3</sup>

This elimination is relatively fast, but not so rapid that therapy results in the adverse, shock-like reactions seen with rapid destruction of large numbers of microfilariae. In addition, subacute removal of microfilariae lessens the chance of macrocyclic lactone resistance, especially when the practitioner is forced to use the slow-kill method due to owner finances or difficulty attaining adulticide (ie, melarsomine).

#### 5. Reduced Lung Reaction to Worm Death (Spontaneous & Postadulticide)

Study 1 also showed that the combination of weekly ivermectin (6 mcg/kg PO) and daily doxycycline (10 mg/kg PO Q 24 H) significantly reduced lung lesions after melarsomine therapy.<sup>3,6</sup>

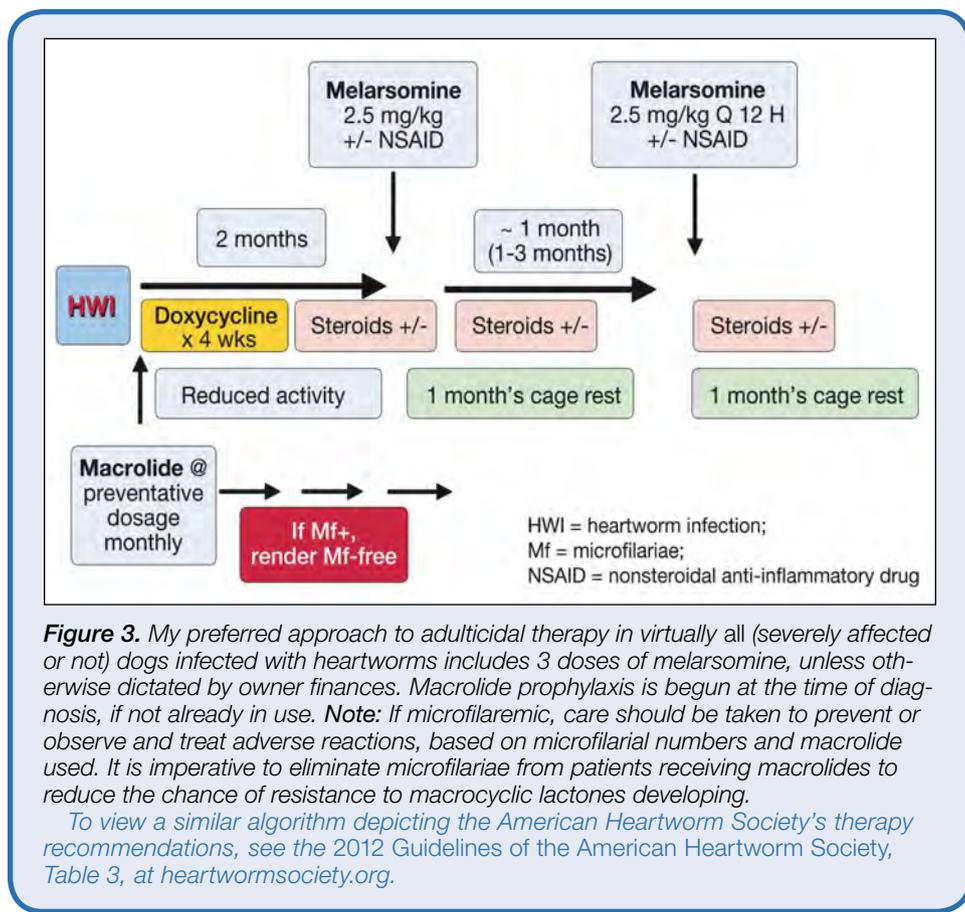
#### 6. Developing Larva Eliminated

Recently, McCall, et al, demonstrated that, while doxycycline (even with ivermectin) does not have rapid adulticidal efficacy, doxycycline monotherapy does stop the progression of infective larvae to adulthood when administered for the first 30 days of infection at 10 mg/kg PO Q 24 H.<sup>7</sup>

- If the 30 days of administration begin on day 40 of infection, however, the effect is partially lost, with

### Should We Worry About Resistance?

Concern has been raised about the potential development of bacterial resistance if doxycycline is administered in all cases of HWD. In my opinion, this concern is worth considering as doxycycline is widely used and valuable to our profession (and physicians) for treatment of a variety of infectious processes. On the other hand, concerns for resistance generally occur when drugs are used at sub-optimal dosages and durations of therapy. Neither of these result from the current treatment recommendations for HWD.



**Figure 3.** My preferred approach to adulticidal therapy in virtually all (severely affected or not) dogs infected with heartworms includes 3 doses of melarsomine, unless otherwise dictated by owner finances. Macrolide prophylaxis is begun at the time of diagnosis, if not already in use. Note: If microfilaremic, care should be taken to prevent or observe and treat adverse reactions, based on microfilarial numbers and macrolide used. It is imperative to eliminate microfilariae from patients receiving macrolides to reduce the chance of resistance to macrocyclic lactones developing.

To view a similar algorithm depicting the American Heartworm Society's therapy recommendations, see the 2012 Guidelines of the American Heartworm Society, Table 3, at [heartwormsociety.org](http://heartwormsociety.org).

2% of L3 reaching adulthood.

- If the larvae reach 65 days before doxycycline is initiated, only 52% reach adulthood.<sup>7</sup>

Therefore, in addition to reducing adverse effects from heartworm death, doxycycline begun on the day of diagnosis will help close the potential seasonal window of continuous infection, which means that, during certain times of year when exposure is continuous (warmest months), the host may have developing larvae of all stages.

### Doxycycline Dosing

Currently the best data we have argues that the dosage, if tolerated, is 10 mg/kg PO Q 12 H for 30 days, administered prior to adulticidal therapy (Figure 3). If this dose is not tolerated, it can be reduced to 5 mg/kg PO Q 12 H.<sup>7</sup>

**Author Recommendation:** I advocate a second month's delay in adulticidal therapy to allow the parasite to deteriorate maximally and, thereby, further reduce the pulmonary reaction to worm death. Benefits include:

- Prevention of maturation of recently acquired infection (tissue phases)
- Reduced pulmonary reaction to dying worms
- More rapid and complete eradication of microfilariae (potentially reducing risk of heartworm resistance to macrocyclic lactones)

- Enhancement of vermucidal efficacy of ivermectin, if using slow-kill method.

### AHS Recommendation:

The American Heartworm Society recommends that, if the slow-kill method is used (only out of necessity), doxycycline should be repeated in 60 days, so the dog receives ivermectin monthly and doxycycline 1 month on, 2 months off, 1 month on, 2 months off, etc, until the antigen test is negative.<sup>8</sup> While there are no data that demonstrate the efficacy of this approach, there are data that indicate recrudescence of *Wolbachia* by 300 days postdoxycycline.<sup>5</sup>

In summary, it appears that doxycycline not only has a role in the management of heartworm infection, but that

this role will continue to grow and be further refined. ■

### Figure Credits

Figure 2. Courtesy Dr. Laura Kramer

Figure 3. Modified from Atkins CE, Miller MW. Is there a better way to administer heartworm adulticidal therapy? *Vet Med* 2003; 98:310-317.

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