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Should We Treat Asymptomatic, Nonproteinuric Lyme-Seropositive Dogs with Antibiotics? No.

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I believe that the decision of whether to treat asymptomatic, nonproteinuric Lyme-seropositive dogs with antibiotics ultimately rests with the individual veterinarian and owner. However, I do not routinely treat these cases, and here's why.

EXPERTS RECOMMEND AGAINST IT

In its Lyme consensus statement,¹ which was based on careful review of the literature and opinions of specialists in the field, the ACVIM did not recommend treating nonclinical, nonproteinuric seropositive animals because there is no evidence that treatment prevents future illness and to avoid antibiotic abuse. Likewise, the authors of a recent review² on canine Lyme borre-

liosis concur that only clinically affected individuals should be treated.

MOST LYME-SEROPOSITIVE DOGS WILL NOT GET SICK

The majority (95%) of Lyme-seropositive dogs will not get sick with Lyme disease.¹ Dogs that are clinically ill or proteinuric should be treated, but based on the ACVIM consensus statement, in some areas 70% to 90% of all healthy dogs were seropositive.¹ Do all these dogs need to be treated? How long would we need to treat them in order to clear them? Not all dogs will be cleared of infection even if they receive 1 month of high-dose doxycycline (20 mg/kg Q 24 H).³

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Should We Treat Asymptomatic, Nonproteinuric Lyme-Seropositive Dogs with Antibiotics? It Depends.

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Whether to treat nonclinical Lyme-positive dogs remains a controversial subject and unfortunately one for which definitive evidence to support either side is lacking. I believe there is no right or wrong answer to this question; in the end, the decision rests with the individual veterinarian and owner.

Lyme disease is an infection most commonly diagnosed and treated by practicing veterinarians in the field and not by academicians or internal medicine specialists. After speaking with veterinarians around the country, I have identified 3 common approaches for these cases.

PATH #1: TREAT THEM ALL

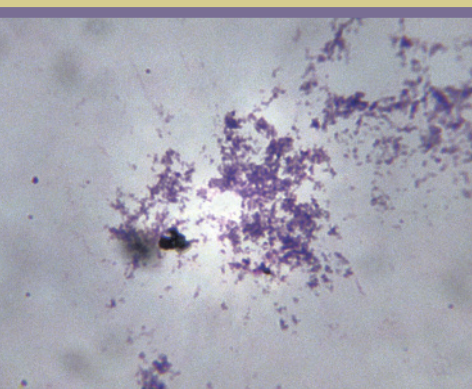
When I asked veterinarians what prompts them to treat all asymptomatic Lyme-positive dogs, the most common answer was, "Why not? What if this dog gets sick down the road or, even worse, develops Lyme nephropathy? I would always wonder if I could have prevented it with treatment, as would the owner."

There are a number of arguments against treatment, including the argument "no proof that it helps," the cost of treatment (minimal), potential side effects of doxycycline (also minimal), and antibiotic overuse. Antibiotic overuse is clearly a topic of national and

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FROM THE DESK OF The Medical Director

Diseases caused by *Borrelia* organisms have been known for decades, with cases identified in Europe since the early 1900s.¹ In the mid-1970s, a cluster of human patients diagnosed with juvenile rheumatoid arthritis in Connecticut led epidemiologists to conclude that a North American *Borrelia* species was causing symptoms that we now know as Lyme disease.²



Borrelia burgdorferi was described in 1983 and soon after (1984 and 1985) it was suggested that *B burgdorferi* was causing clinical illness in dogs.³ The clinical syndromes most commonly associated with Lyme disease in dogs include polyarthritis and glomerulopathy. Most humans exposed to *B burgdorferi* show clinical signs in contrast to the 95% of exposed dogs

that remain asymptomatic.³ Puppies experimentally infected with *B burgdorferi* had transient fever, anorexia, and arthritis; they are the only canine models fulfilling Koch's postulates.

Experimental models have failed to confirm the clinical picture associated with *B burgdorferi* infection of renal, cardiac, neurologic, or dermatologic manifestations, although these have been reported in the field.³ There are numerous reports of glomerulonephritis with protein loss, which probably is an immune-mediated phenomenon.³

Because *B burgdorferi* is a tick-borne pathogen, potential coinfection with other tick-borne diseases that may cause or exacerbate the clinical picture should be considered.⁴

Patricia Thomblison, DVM, MS

1. Emerging tick-borne diseases. Fritz CL. *Vet Clin North Am* 39:265-278, 2009.
2. Lyme arthritis: An epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Steere AC, Malawista SE, Snydman DR, et al. *Arthritis Rheum* 20:7-17, 1977.
3. ACVIM Small Animal Consensus Statement on Lyme Disease in Dogs: Diagnosis, treatment, and prevention. Littman MP, Goldstein RE, Labato MA, et al. *J Vet Intern Med* 20:422-434, 2006.
4. Lyme borreliosis in dogs and cats: Background, diagnosis, treatment and prevention of infections with *Borrelia burgdorferi sensu stricto*. Krupka I, Straubinger FK. *Vet Clin North Am* 40:1103-1119, 2010.

NO CONTINUED

An experimental tick exposure model^{1,4} of Lyme disease in beagles demonstrated that 6- to 12-week-old exposed pups had a 4-day self-limiting illness characterized by lameness, anorexia, and fever approximately 2 to 5 months postexposure; these pups possibly had several shorter bouts of illness several weeks apart. In addition, 12- to 26-week-old exposed pups had fewer and milder signs, while older exposed pups and adults seroconverted but showed no clinical signs. This suggested that Lyme disease was not a serious disease requiring treatment. I do recommend treating seropositive pets that have clinical signs, but I see no reason to treat the vast majority of seropositive dogs that are not showing signs.

IT DEPENDS CONTINUED

global importance, but how important is it to a dog owner who understands the seriousness of Lyme disease? Is it wrong to deny this owner therapy that may reduce the risk for clinical Lyme disease or even Lyme nephritis in his or her pet?

PATH #2: DO NOT TREAT ANY ASYMPTOMATIC PETS

The evidence-based approach suggests that beneficial treatment of asymptomatic pets has not been documented. This is an approach with solid scientific grounds and one that is clearly valid.

LYME IS OVERDIAGNOSED & OVERTREATED

Lyme disease is overdiagnosed and overtreated even in symptomatic seropositive animals. Dogs may respond to doxycycline treatment because of coinfections, coincidence, or doxycycline antiinflammatory properties.¹ In one study, non-Lyme-related causes of clinical signs were identified in 40% of dogs originally diagnosed with Lyme disease.⁵

LYME QUANTITATIVE C₆ TEST

I administer the Lyme quantitative C₆ titer (Lyme Quantitative C₆ Antibody Test, idexx.com) in symptomatic seropositive dogs. If the pet is treated, I repeat the test 6 months later to obtain a new baseline.

However, there is minimal evidence that the magnitude of the quantitative C₆ titers will predict illness or that treatment decisions should be based on these

titers. Many asymptomatic dogs have very high quantitative C₆ titers, including asymptomatic beagles in the experimental tick model.⁶ In a field study, asymptomatic dogs had quantitative C₆ titers as high as 614 U/mL, while untreated control dogs with high quantitative C₆ titers did not develop clinical Lyme disease during a 12-month observation period.⁷

LYME NEPHROPATHY & OTHER CONSIDERATIONS

Lyme nephropathy was not seen in the experimental model of Lyme disease in dogs.¹ Lyme nephropathy is associated with Lyme-specific antigen-antibody

complexes and causes immune-mediated glomerulonephritis and protein-losing nephropathy.^{1,8,9} In the field, Lyme nephropathy is a serious but rare sequela even in breeds in which it is most commonly seen (Labrador and golden retrievers).

Most Lyme-seropositive retrievers are nonproteinuric.¹⁰ No predictive tests indicate which seropositive dogs will become proteinuric. More research is required to determine the pathogenesis of this entity. This includes the potential for a genetic podocytopathy or immunodysregulation causing entrapment of

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I do not routinely treat asymptomatic seropositive dogs, but I might be convinced to treat a nonclinical retriever if the owner is worried about Lyme nephropathy, even though there is no evidence of benefit.

PATH #3: TAKE A MIDDLE-ROAD APPROACH

It is my impression that the majority of practitioners in Lyme-endemic areas take a “middle-road approach.” Treating every dog may be overzealous, particularly when the same dog is Lyme positive year after year, potentially from the same initial infection.

The middle-road approach suggests that the clinician should consider whether there is even partial evidence that certain asymptomatic dogs might benefit from

therapy.¹ If so, is there a way to select individual cases that might benefit from treatment? What tools do we have to make that determination?

Measure Proteinuria

Proteinuria is the first parameter that I suggest for selecting which patients to treat. The ACVIM Lyme consensus statement² recommends (and I concur) that proteinuric dogs should be treated because of fear of early Lyme nephritis.

However, it is important to recognize that many, if not most, of these dogs may be proteinuric from other causes.

Use the Lyme Quantitative C₆ Test

Although there is no definitive evidence that a high quantitative C₆ antibody titer predicts clinical disease in the future or that drops in titer predict less clinical disease, the Lyme Quantitative C₆ Antibody Test (idexx.com) may be a legitimate decision-making tool. Such studies

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When clients ask me what I recommend or how I would treat my own pet, I outline the available options, explain that we do not know what the right answer is, and suggest taking a middle-road approach.

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circulating immune complexes, prevention by treatment and/or Lyme vaccination, whether dogs may show immune sensitization, or if a Jarisch-Herxheimer reaction (a heightened illness resulting from release of antigens and toxins from dead spirochetes) is ever seen.

I do not routinely treat asymptomatic seropositive dogs, but I might be convinced to treat a nonclinical retriever if the owner is worried about Lyme nephropathy, even though there is no evidence of benefit. Treatment does not guarantee clearance of infection or that the dog will not become proteinuric, so monitoring for proteinuria is essential whether dogs are treated or not.

In a 2009 study, seropositive Bernese mountain dogs showed no tendency for future lameness, azotemia, or proteinuria over a 2.5- to 3-year observation period.¹¹

ANTIBIOTIC CONCERNS

Doxycycline, although inexpensive and usually safe, can cause side effects in dogs, including increased liver enzymes (35%–40%), vomiting/regurgitation (18%), diarrhea (7%), and anorexia (2.5%).¹² Other antibiotics used to treat Lyme disease (amoxicillin, erythromycin, azithromycin) have their own side effects; but because they are not used to treat possible coinfections, these antibiotics would not be my first choice if I were to treat a dog for Lyme disease. Finally, overuse of antibiotics likely promotes environmental bacterial resistance.

CLOSING REMARKS

So if I do not routinely treat nonclinical Lyme-seropositive dogs, why do I routinely recommend the SNAP 4Dx Test (idexx.com) for dogs with and without

clinical signs in endemic and nearby areas? What do I tell the owner of a healthy dog that has Lyme antibodies due to natural exposure?

Knowing the seroprevalence in healthy dogs in our area helps me better appreciate the background “noise” and consider coinfections and other differentials in symptomatic dogs. Screening helps educate owners about Lyme disease, coinfections, public health aspects of tick-borne diseases, and the importance of using tick control and screening tests for proteinuria.¹

See Aids & Resources, back page, for references & suggested reading.

IT DEPENDS CONTINUED

have not been performed and would require prospective evaluation of many treated and untreated dogs in the field. Therefore, what evidence do we have to support the use of quantitative C₆ titers in deciding whether to treat Lyme-positive dogs? Here's what we know:

- Quantitative C₆ titers may drop more rapidly with therapy than without in dogs, particularly if the initial titer is above a certain threshold.³
- A posttreatment drop in quantitative C₆ titers is associated with a more positive clinical outcome in humans.⁴
- Quantitative C₆ titers correlate with circulating immune complexes in

Lyme-positive dogs, and a drop in the titer predicts a drop in immune complexes.⁵

We do not know whether a drop in quantitative C₆ titers or circulating immune complexes means decreased likelihood of future disease or Lyme nephritis; this study has not been performed on a large enough scale to achieve a definitive answer. In my opinion, however, until such a study is done, use of quantitative C₆ titers is a reasonable, logical approach to decision making for veterinarians and owners. And, pending additional data, I would use it as well.

CLOSING REMARKS

In the end, there is no definitive conclusion or correct answer to this question. At Cornell, we do treat nonclinical dogs at the owner's request after discussing the risks and benefits associated with therapy. When clients ask me what I recommend or how I would treat my own pet, I outline the available options, explain that we don't know what the right answer is, and suggest taking a middle-road approach, citing proteinuria and quantitative C₆ titers as possibly the best decision-making tools we have right now.

See Aids & Resources, back page, for references & suggested reading.