

# DIAGNOSTIC INSIGHTS

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## Is it Lyme disease, anaplasmosis—or or both?



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Lyme disease and anaplasmosis (formerly known as granulocytic ehrlichiosis) are caused by different infectious organisms—*Borrelia burgdorferi* and *Anaplasma phagocytophilum*, respectively. Both diseases, however, share the same vector: ticks. In the Midwest, Northeast, and Southeast United States, the specific vector is the *Ixodes scapularis* tick. On the West Coast, it's the *Ixodes pacificus* tick. The white-footed mouse, *Peromyscus leucopus*, is often the mutual reservoir host for both organisms, particularly in the Northeast and upper Midwest.

Dogs diagnosed with canine anaplasmosis can exhibit clinical signs similar to those found with Lyme disease (*i.e.*, polyarthritis, fever, lameness, lethargy, anorexia, and lymphadenopathy), as well as uveitis and thrombocytopenia, with morulae found in the neutrophils of peripheral blood or synovial fluid. Many

dogs diagnosed with Lyme disease, based on the clinical signs and serologic findings, may well be demonstrating signs of infection with *Anaplasma* or coinfection with both organisms.

Furthermore, the laboratory models used to characterize canine Lyme disease have involved field-caught *I. scapularis* ticks from the Northeast, which were likely co-infected. Therefore, the models may to some extent be models of coinfection-induced disease.

In addition, when field-caught ticks were used to challenge dogs immunized with various Lyme disease vaccines, these dogs were often being challenged unknowingly with

multiple tick-borne organisms. Early reports of dogs immunized against Lyme disease but displaying signs of the illness (without Western blot evidence of *B. burgdorferi* infection) may have been describing canine anaplasmosis in naturally exposed dogs.

That raises the question posed in the title above: Is it Lyme disease, anaplasmosis, or both? Fortunately, a new test from IDEXX Laboratories—the SNAP 4Dx—helps veterinarians answer that question quickly.

### Coinfection studies

One of the first studies to suggest the possibility of coinfection in dogs was conducted in the mid-1980s. Using

**Table 1: Incidence of Single and Coinfection with *A. phagocytophilum* and *B. burgdorferi***

Time of sample collection	<i>A. phagocytophilum</i> -positive/ <i>B. burgdorferi</i> -negative samples	<i>A. phagocytophilum</i> -positive/ <i>B. burgdorferi</i> -positive samples
1985 and 1986	0%	15.6%
2001	6.6%	40%
2002 to 2004	23.8%	45.9%

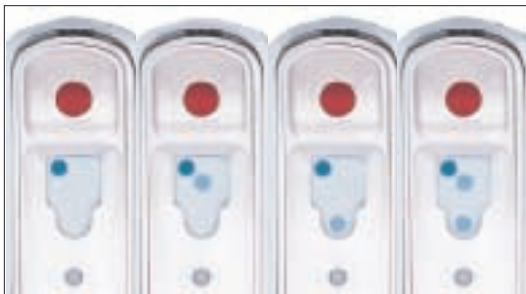


Photo: IDEXX Laboratories

The IDEXX SNAP 4Dx test with four different results. From left: negative for *A. phagocytophilum* and *B. burgdorferi*, positive for *A. phagocytophilum*, positive for *B. burgdorferi*, and positive for both *A. phagocytophilum* and *B. burgdorferi*.



Photo: Kirby Starford III, PhD

The white-footed mouse is the reservoir host for *B. burgdorferi* and *A. phagocytophilum*. Immature *Ixodes scapularis* feed on coinfecting mice and then coinfect dogs.



Photo: Steve Levy, VMD

A Brittany spaniel diagnosed with Lyme disease in the mid-1980s. The swollen hock is typical of both Lyme disease and anaplasmosis, and this dog may have been coinfecting.



Photo: Pfizer Animal Health

*Ixodes scapularis*, from left: larva, nymph, adult female, and adult male. All ticks are "flat," or unfed.

clinically ill dogs, the study found that 15.6% (10 of 64) of dogs infected with *B. burgdorferi* and 0% (0 of 42) of dogs negative for *B. burgdorferi* had antibodies to *A. phagocytophilum* (formerly *Ehrlichia equi*).<sup>1</sup>

In a 2001 pilot study, I tested clinically normal dogs in myConnecticut practice using the SNAP 3Dx test and identified 15 *B. burgdorferi*-positive dogs and 15 negative dogs. Each dog was then tested for antibodies to *A.*

*phagocytophilum*. Forty percent (6 of 15) of the *B. burgdorferi*-positive dogs were also infected with *A. phagocytophilum*, and 6.6% (1 of 15) of the *B. burgdorferi*-negative dogs were positive for *A. phagocytophilum*.<sup>2</sup>

Since then, coinfections have continued to increase (Table 1). In 2002, 2003, and 2004, I collected and froze serum or plasma from 621 dogs in my practice that tested positive for *B. burgdorferi* infection using a SNAP

3Dx test. In 2005, these samples were tested for *A. phagocytophilum* antibodies to determine the incidence of single and coinfections. Single infection with *A. phagocytophilum* was found in 23.8% (148 of 621), single infection with *B. burgdorferi* was found in 13.8% (86 of 621), and of the 159 dogs that tested positive for *B. burgdorferi* infections, 45.9% (73 of 159) were coinfecting with *A. phagocytophilum*.

Before the IDEXX SNAP 4Dx test became available, identifying *A. phagocytophilum* as a sole or coinfecting agent was cumbersome. The samples had to be sent to a reference laboratory for serology or examination of peripheral blood smears to detect morulae in the neutrophils. Oftentimes, coinfection status was determined long after antibiotic therapy, when frozen samples were analyzed for research and development projects.

## Tick disease timeline

Tick-borne diseases of dogs and people have been emerging as clinical syndromes in the past two decades. Here is a recap of important dates in the history of the study of these diseases.

Because so many of the Lyme-positive dogs I tested were later determined also to be *Anaplasma*-positive, it is clear that I treated many dogs infected with *A. phagocytophilum* without knowing the dogs' true infection status—there was as yet no rapid assay available to detect *A. phagocytophilum*. This highlights the confounding factor coinfection adds to the various studies (*i.e.*, clinical, diagnostic, therapeutic, and vaccine-related) on Lyme disease. Fortunately, the development of the IDEXX SNAP 4Dx test has made it easier to diagnose coinfections and collect data on canine populations.

### Treatment considerations

In patients with arthritis-like signs, infections from both *B. burgdorferi* and *A. phagocytophilum* may respond to doxycycline treatment (5 to 10 mg/kg given orally with food twice a day—I prefer the higher end of the dose range). However, severe protein-losing

Thus emerged the taxonomy of the two major pathogens vectored by *I. scapularis* and *Ixodes pacificus* ticks, and the names “Lyme disease” and “anaplasmosis” (formerly granulocytic ehrlichiosis) have become associated with clinical syndromes caused by these pathogens. However, it is becoming clear that many individuals thought to have a single infection were actually infected with both pathogens, and clinicians are beginning to investigate the clinical significance of coinfection.

**1975** Lyme arthritis was first noted as a clinical entity in people in Old Lyme, Conn., and two adjacent communities.<sup>1</sup>

**1982** Willy Burgdorfer, PhD, discovered the etiologic organism in an *Ixodes dammini* (later renamed *Ixodes scapularis*) tick from Long Island, N.Y.<sup>2</sup>

**1984** The first case of canine Lyme arthritis was reported.<sup>3</sup>

**1986** Steve Levy, VMD, diagnosed the first case of canine Lyme carditis.<sup>4</sup> A fatal renal syndrome began emerging in *Borrelia burgdorferi*-infected dogs in his practice.<sup>5,6</sup>

**1994** Twelve people were reported to have human granulocytic ehrlichiosis.<sup>7</sup> All 12 patients had morulae in the cytoplasm of neutrophils but none were detected in mononuclear white blood cells. Eight of 10 patients and seven of 10 patients tested had antibody titers of 1:80 or greater directed against *Ehrlichia phagocytophila* and *Ehrlichia equi*, respectively. Serologic assays and PCR data supported the conclusion that all 12 patients were infected with *E. phagocytophila*, *E. equi*, or closely related *Ehrlichia* species.

**1997** Analysis of frozen sera collected in the mid-1980s from Northeastern dogs demonstrating clinical signs associated with leukopenia, thrombocytopenia, and anemia revealed antibodies directed against *E. equi*.

**2001** Genetic analysis was used to reclassify *E. phagocytophila*, *E. equi*, and the human granulocytic ehrlichiosis organism as a single organism now called *Anaplasma phagocytophilum*.<sup>8</sup>

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nephropathy associated with canine Lyme disease is generally not responsive to antibiotic therapy and is often fatal. Dogs that develop uveitis from *A. phagocytophilum* infections have responded to oral doxycycline and nonsteroidal anti-inflammatory drugs, as well as topical ophthalmic indo-

methacin and antibiotic-corticosteroid therapy, a protocol developed in consultation with a veterinary ophthalmologist. In my practice, all dogs infected with *B. burgdorferi* and *A. phagocytophilum* are treated with doxycycline.

### Conclusion

The increase in the number of dogs infected with *B. burgdorferi* and *A. phagocytophilum* is caused by several factors: the expanding range of the tick vectors, increased travel by pet owners with their dogs, and a tendency for families to move into tick-laden environments. In addition, these organisms' shared vector and reservoir host also increase the threat of coinfection. The SNAP 4Dx test, which

indicates a dog's infection status for both *B. burgdorferi* and *A. phagocytophilum*, will help veterinarians determine if one or both bacteria are present. This may not change the treatment, but it may improve our understanding of the clinical signs in each type of infection. Finding coinfection may also lead veterinarians to consider a larger spectrum of diseases vectored by *Ixodes*-genus ticks.

### References

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