How, When, & Whether to Treat Subclinical Rickettsial Disease

Meryl P. Littman, VMD, DACVIM
University of Pennsylvania

You have asked…

How should we manage subclinical dogs that are seropositive for rickettsial diseases?

The expert says…

Popular combined screening tests, such as SNAP 4Dx Plus (idexx.com) and AccuPlex4 (antechdiagnostics.com), can help identify healthy subclinical (nonclinical) dogs seropositive for rickettsial agents by assaying for heartworm antigen and for antibodies against Lyme disease (*Borrelia burgdorferi*), anaplasmosis (*Anaplasma phagocytophilum*), and ehrlichiosis (*Ehrlichia canis*). In addition, the SNAP 4Dx Plus test identifies antibodies against *E chaffeensis, E ewingii, A platys*, and a novel *E muris*-like agent found in dogs.[1,2] *Anaplasma* and *Ehrlichia* organisms may also be associated with carrier status both in untreated exposed dogs and in treated dogs.

Whether to give antibiotics to dogs with subclinical, nonproteinuric Lyme-seropositivity has been debated[3-6]; the consensus appears to be *no*, although such dogs should be monitored for occult proteinuria. Meanwhile, how should subclinical *Anaplasma* spp and/or *Ehrlichia* spp seropositive dogs be clinically managed? Might they still be carriers, and might carriers become clinically ill in the future? Can the carrier state be cleared, and can seropositive dogs be used safely as blood donors? Do these dogs remain potential reservoirs for infection of other animals and humans?

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Clinical Cues

Certain rickettsial organisms parasitize granulocytic (*A phagocytophilum, E ewingii*) or mononuclear (*E canis, E chaffeensis*) WBCs or platelets (*A platys*). Signs in infected dogs vary (see **Clinical Signs of Rickettsial Infection**, next page),[7-11] and infection may result in chronic carrier states with no sign of clinical illness.

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Diagnostic tests may reveal cytopenias (eg, thrombocytopenia, possible anemia and/or leukopenia), basophilic cytoplasmic inclusion bodies (morulae) in WBCs or platelets (via synovial fluid cytology or peripheral blood or buffy coat smears), renal proteinuria with negative urine culture, hypoalbuminemia, hyperglobulinemia with polyclonal or monoclonal gammopathy, hypercholesterolemia, and possibly elevated liver enzymes.[7-11]

To Treat or Not to Treat?

For seropositive dogs with illness suggestive of rickettsial disease, treatment with doxycycline at 5 mg/kg q12h or 10 mg/kg q24h for 28 days is recommended; dogs with acute or mild to moderate illness generally respond within 1 or 2 days of antibiotics.[7-11] Quantitative IFA or ELISA testing may be used to assess response to therapy and establish baselines for future comparisons at 0 and 6 to 12 months posttreatment, particularly if signs recur or worsen. Decreased titers or normalization of hematologic/urinalysis abnormalities may indicate organism clearance or decreased antigenic burden.

But should we routinely treat subclinical seropositive dogs with doxycycline?

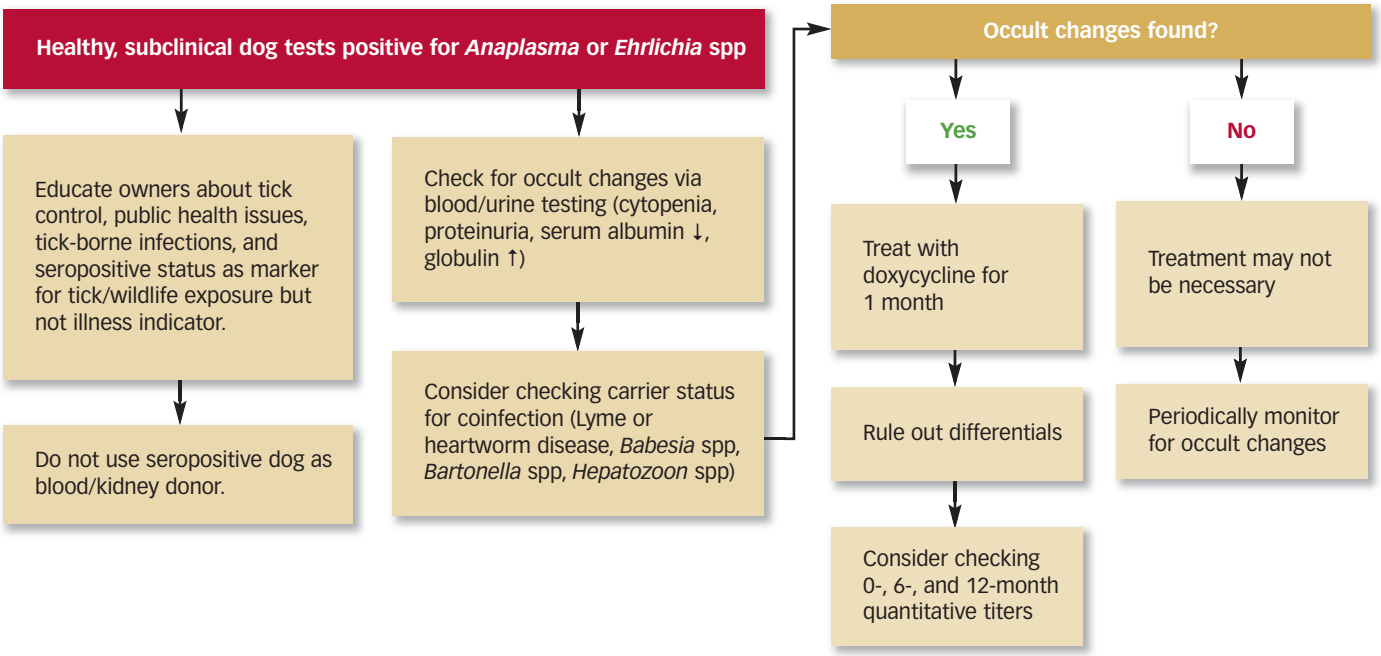
The author's answer is *no*; however, occult clinicopathologic changes such as cytopenias (eg, anemia, leukopenia, thrombocytopenia), proteinuria, hypoalbuminemia, or hyperglobulinemia should be evaluated (see **Management Plan for Subclinical Seropositive Dogs**). Abnormalities necessitate antimicrobial treatment, and further investigation may be indicated to rule out other causes of these changes, including coinfection with other infectious diseases, as seropositivity may be a coincidence or a marker for tick and wildlife exposure. Additional testing for heartworm antigen and antibodies against *B burgdorferi, Babesia* spp, *Bartonella* spp, *Leptospira* spp, *Hepatozoon* spp, *Brucella* spp, or *Leishmania* spp may be indicated.

Clinical Signs of Rickettsial Infection

Can include[7-11]:

- Lethargy
- Depression
- Anorexia
- Fever
- Lameness (polyarthropathy, myopathy)
- Lymphadenopathy
- Hepatosplenomegaly
- Hemorrhages
- Neurologic signs secondary to meningitis
- Uveitis and ocular changes
- Vasculitis
- Edema or effusion
- Oculonasal discharge
- Vomiting and/or diarrhea
- Pruritus
- Pneumonitis ± cough
- Protein-losing nephropathy (± hypertension)
- Thromboembolic events

Management Plan for Subclinical Seropositive Dogs



Why Not?

This clinical rationale for management (not treatment) of subclinical seropositive dogs with no clinicopathologic abnormalities is sevenfold:

1 Seropositivity proves exposure only, not necessarily active infection or carrier status. A dog can remain seropositive even after previous treatment or after infection has cleared.[7-12]

2 Many exposed dogs remain healthy and either do not become ill or have mild disease that does not necessitate treatment.[7-12] In experimental studies, beagle puppies and adults were exposed to *Ixodes* ticks and observed for over a year.[13-15] Adult dogs showed no signs of illness; however, puppies exposed at 6 to 12 weeks of age showed self-limiting lameness, anorexia, and fever but did not require treatment. These studies were meant to investigate Lyme disease, but 35% to 45% of the dogs were inadvertently coinfected, demonstrating antibodies against both *B burgdorferi* and *A phagocytophilum* (some were also seropositive to *Babesia microti*).[13-15] In an experimental *E canis* infection model, beagles became chronic carriers but did not show the severe bone marrow hypoplasia demonstrated in German shepherd dogs with breed-associated reduced cellular immune responses.[16]

3 Serosurveys show that a high percentage of clinically healthy dogs have antibodies against *Ehrlichia* spp.[7] No differences for seroprevalence against *Anaplasma* spp were found between healthy and sick dogs in Minnesota[17] or Pennsylvania[18]; however, Lyme and *Anaplasma* spp coinfection appeared to increase risk for illness.[17]

4 Treatment may not clear the carrier state, and organisms can remain despite doxycycline therapy. *E canis* organisms were found in splenic aspirates after 6 weeks of doxycycline treatment.[7,12] Likewise, doxycycline may not clear all *Anaplasma* spp carriers[10]; *A phagocytophilum* PCR tests were negative during and after treatment in another study, although lack of clearance was proven when PCR tests became positive again after corticosteroid challenge.[19,20]

5 Because immunity to these agents is not long lasting, dogs may be reexposed and become reinfected without proper tick control. Titers may persist or become negative after treatment.[7-12] It is possible that carrier status actually protects dogs from becoming ill from reexposure and acute illness.

6 Abusing or misusing doxycycline, not as inexpensive as it was previously, may have adverse effects to both the individual and environment. Although doxycycline is typically safe, GI signs in up to 18% and elevated liver values in up to 40% of treated dogs have been reported.[21] Furthermore, veterinarians should not overuse antibiotics, to avoid increasing bacterial resistance and compromise doxycycline efficacy.

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7 Depending on the duration and magnitude of rickettsemia, carrier dogs may act as potential reservoirs for infection. Wildlife reservoirs are more important for organisms carried by *Ixodes* and *Amblyomma* ticks (eg, *A phagocytophilum, E chaffeensis*), but as all stages of *Rhipicephalus* spp ticks feed on dogs, dogs are the main reservoirs for *E canis* and other organisms carried by these ticks (eg, *Babesia* spp). As antimicrobials may not clear carriers, tick control remains the most important tool to prevent ticks from picking up infection from carriers and infecting new hosts.

Why Screen Without Intent to Treat?

Seropositive dogs are sentinels and help educate owners about public health issues, tick-borne disease, and whether tick prevention efforts are adequate. Awareness of the background seroprevalence of these infections in a practice's region can prevent overdiagnosis in these and other cases. Screening for occult changes (eg, proteinuria, cytopenias) in seropositive subclinical dogs allows early intervention when it is likely to be most helpful. ■ cb

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

For More

For a debate between two authors, read **A Matter of Opinion: Should We Treat Asymptomatic Nonproteinuric Lyme-Seropositive Dogs with Antibiotics?** by Drs. Meryl P. Littman & Richard E. Goldstein at **cliniciansbrief.com/matter-of-opinion-lyme**