

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 debated³⁻⁶; 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?

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.

MORE ►

Do these dogs remain potential reservoirs for infection of other animals and humans?

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.

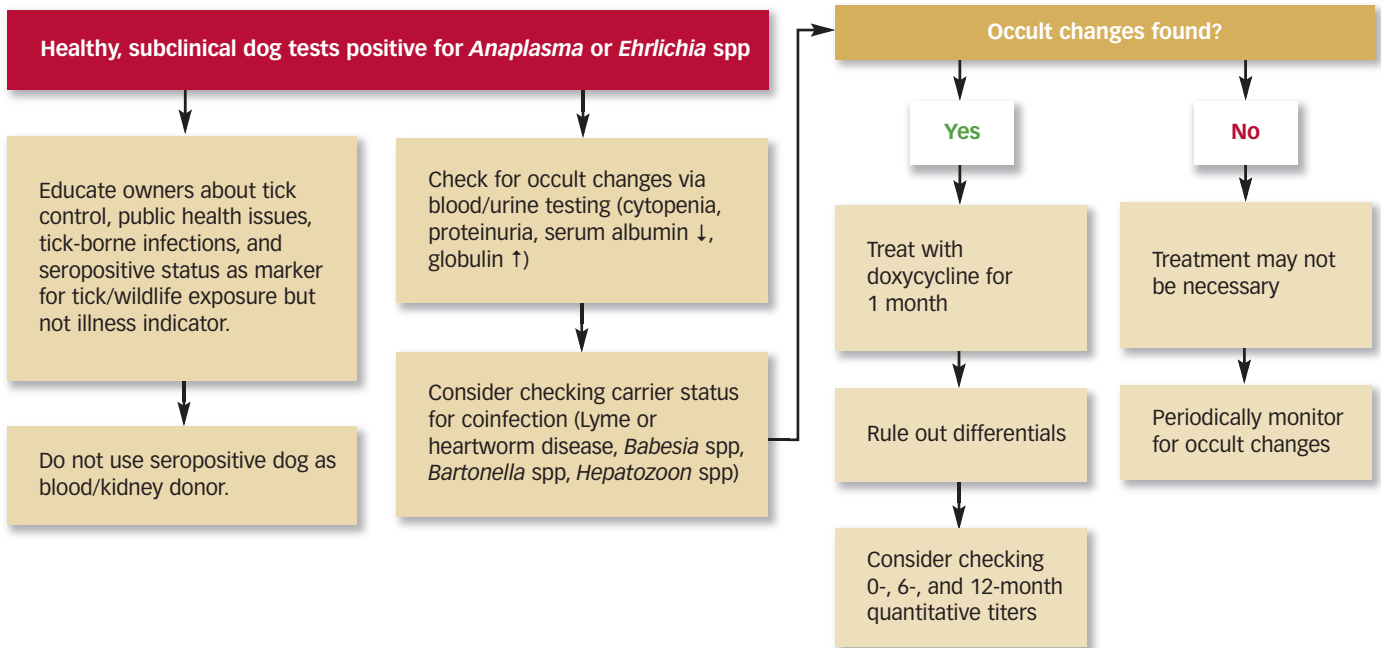


Clinical Signs of Rickettsial Infection

Can include⁷⁻¹¹:

- 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 coinfecting, 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 Minnesota¹⁷ or Pennsylvania¹⁸; 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 carriers¹⁰; *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.

MORE ►

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

COMFORTIS®-Cats (spinosad)

Chewable Tablets
Before using COMFORTIS chewable tablets, please consult the product insert, a summary of which follows:
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
Indications: COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*), for one month, on cats and kittens 14 weeks of age and older and two pounds of body weight or greater.
Dosage and Administration: COMFORTIS is given orally once a month, at the minimum dosage of 22.5 mg/lb (50 mg/kg). Administer COMFORTIS with food for maximum effectiveness. If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.
Contraindications: There are no known contraindications for the use of COMFORTIS.
Warnings: Not for human use. Keep this and all drugs out of the reach of children.
Precautions: Use with caution with concomitant extra-label use of ivermectin. The safe use of COMFORTIS in breeding, pregnant, or lactating cats has not been evaluated.

Adverse Reactions: In a well-controlled US field study, which included a total of 211 cats (139 treated with COMFORTIS and 72 treated with an active topical control once a month for 3 treatments), no serious adverse reactions were attributed to the administration of COMFORTIS. The most frequently reported adverse reaction in cats was vomiting.

Percentage of Cats (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	COMFORTIS (n=139)	Active Topical Control (n=72)	COMFORTIS (n=135)	Active Topical Control (n=69)	COMFORTIS (n=132)	Active Topical Control (n=67)
Vomiting	14.4	1.4	14.8	1.4	13.6	4.5
Lethargy	3.6	0	0.7	0	1.5	1.5
Anorexia	2.2	0	0.7	0	2.3	1.5
Weight Loss	1.4	0	0	0	3	0
Diarrhea	1.4	1.4	0.7	2.9	2.3	1.5

Over the 3-month (3-dose) study, vomiting occurred on the day of or the day after at least one dose in 28.1% (39/139) of the cats treated with COMFORTIS and in 2.8% (2/72) of the cats treated with the active topical control. Three of the 139 cats treated with COMFORTIS vomited on the day of or the day after all three doses. Two cats that received extra-label topical ivermectin on Day -1 of the field study developed lethargy on Day 1 after COMFORTIS administration on Day 0. For technical assistance or to report an adverse drug experience, call Elanco at 1-888-545-5973. Additional information can be found at www.comfortis.com. For a complete listing of adverse reactions for spinosad reported to the Center for Veterinary Medicine, see Adverse Drug Experience Reports under <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation>

Effectiveness: In a well-controlled laboratory study, COMFORTIS began to kill fleas 30 minutes after administration and demonstrated 98% effectiveness within 4 hours. COMFORTIS kills fleas before they can lay eggs. In a separate well-controlled laboratory study, COMFORTIS demonstrated 100% effectiveness on the first day following treatment and ~90% effectiveness on Day 30. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In a field study conducted in households with existing flea infestations, flea count reductions of 97.5% were observed one month after the first treatment and 99.3% after three monthly treatments with COMFORTIS. Cats with pre-existing signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis, and pruritus as a direct result of eliminating the fleas.

Storage Information: Store at 20 to 25°C (68 to 77°F), excursions permitted between 15 to 30°C (59 to 86°F).

How Supplied: COMFORTIS is available in four tablet sizes for use in cats: 90, 140, 270 or 560 mg. Each tablet size is available in color-coded packages of 6 tablets.

NADA #141-277, Approved by the FDA
Manufactured by Elanco Animal Health, A Division of Eli Lilly and Company, Indianapolis, IN 46285

COMFORTIS®-Dogs (spinosad)

Chewable Tablets
Before using COMFORTIS chewable tablets, please consult the product insert, a summary of which follows:
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
Indications: COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*) for one month, on dogs and puppies 14 weeks of age and older and 3.3 pounds of body weight or greater.
Dosage and Administration: COMFORTIS is given orally once a month, at the recommended minimum dosage of 13.5 mg/lb (30 mg/kg). Administer COMFORTIS with food for maximum effectiveness. If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.
Contraindications: There are no known contraindications for the use of COMFORTIS.
Warnings: Not for human use. Keep this and all drugs out of the reach of children. Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with COMFORTIS (see POST APPROVAL EXPERIENCE).
Precautions: COMFORTIS is for use in dogs and puppies 14 weeks of age and older. Use with caution in breeding females and in dogs with pre-existing epilepsy. The safe use of COMFORTIS in breeding males has not been evaluated.

Adverse Reactions: In a well-controlled US field study, which included a total of 470 dogs (330 dogs treated with COMFORTIS and 140 dogs treated with an active control), no serious adverse reactions were observed with COMFORTIS. All reactions were regarded as mild and did not result in any dog being removed from the study. The most frequently reported adverse reaction in dogs in the COMFORTIS and active control groups was vomiting. The occurrence of vomiting, most commonly within 48 hours after treatment, decreased with repeated doses of COMFORTIS.

Percentage of Dogs (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	COMFORTIS Chewable Tablets (N=330)	Active Topical Control (N=139)	COMFORTIS Chewable Tablets (N=282)	Active Topical Control (N=124)	COMFORTIS Chewable Tablets (N=260)	Active Topical Control (N=125)
Vomiting	12.7	12.2	7.8	3.2	5.8	4.8
Decreased Appetite	9.1	5	2.8	1.6	1.9	0.8
Lethargy	7.6	5	3.5	4	1.2	0.8
Diarrhea	6.7	5	4.3	0.8	1.2	0
Cough	3.9	5	0.4	2.4	0	0
Polydipsia	2.4	1.4	0.7	0	0.4	0
Vocalization	1.8	0	0.4	0	0.4	0
Increased Appetite	1.5	0	0.4	0.8	0.4	0
Erythema	1.5	0	0.4	0	0.4	0
Hypersalivation	1.2	1.4	0	0	0.4	0
Excessive Salivation	1.2	0	0.4	0	0	0

¹ This number (n=139) is less than the total number of dogs in the safety population for the active control group (n=140) because one dog joined the study late and was only dosed at Month 3. In US and European field studies, no dogs experienced seizures when dosed with COMFORTIS at the therapeutic dose range of 13.5-27.3 mg/lb (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that received higher than the maximum recommended dose of 27.3 mg/lb (60 mg/kg) experienced at least one seizure within the week following the second dose of COMFORTIS, but no seizures following the first and third doses. The cause of the seizures observed in the field studies could not be determined.

Post Approval Experience (June 2009): The following adverse reactions are based on post-approval adverse drug event reporting. The adverse reactions are listed in decreasing order of frequency: vomiting, depression/lethargy, anorexia, ataxia, diarrhea, pruritus, trembling, hypersalivation and seizures. Following concomitant extra-label use of ivermectin with COMFORTIS, some dogs have experienced the following clinical signs: trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation. Post approval experience continues to support the safety of COMFORTIS when used concurrently with heartworm preventatives according to label directions.

For technical assistance or to report an adverse drug experience, call Elanco at 1-888-545-5973. Additional information can be found at www.comfortis.com. For a complete listing of adverse reactions for spinosad reported to the Center for Veterinary Medicine, see Adverse Drug Experience Reports under <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation>.

Effectiveness: In a well-controlled laboratory study, COMFORTIS began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. COMFORTIS kills fleas before they can lay eggs. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In field studies conducted in households with existing flea infestations of varying severity, flea reductions of 98.0% to 99.8% were observed over the course of 3 monthly treatments with COMFORTIS. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis and pruritus as a direct result of eliminating the fleas.

Storage Information: Store at 20-25°C (68-77°F), excursions permitted between 15 to 30°C (59 to 86°F).

How Supplied: COMFORTIS is available in six tablet sizes for use in dogs: 90, 140, 270, 560, 810 or 1620 mg. Each tablet size is available in color-coded packages of 6 tablets.

NADA #141-277, Approved by the FDA
Manufactured by Elanco Animal Health, A Division of Eli Lilly and Company, Indianapolis, IN 46285