Ehrlichia bacteria are obligate intracellular members of the family Anaplasmataceae, and several species are capable of causing infection, with or without illness, in dogs. The first species described was Ehrlichia canis, which is still of enormous importance to the health of dogs worldwide. Additionally, Ehrlichia ewingii is a common cause of low-mortality, moderate-morbidity infection in much of the United States. Ehrlichia chaffeensis is the pathogen responsible for human monocytic ehrlichiosis, and while dogs can become infected and mount potentially cross-reactive antibody responses, it seems to cause very little disease in dogs. Other species of Ehrlichia infect dogs on occasion (e.g., Panola Mountain Ehrlichia, Ehrlichia muris eauclairensis).

When a routine screening test for Ehrlichia returns a positive result in an apparently healthy dog, treatment with antimicrobials is not automatically the appropriate course of action. The decision of what course of action to pursue depends on several factors.

**IMPORTANT EHRlichia SPECIES**

Three Ehrlichia species are important for small animal veterinarians to understand (Table 1).

E canis can cause an acute febrile illness, often followed by a prolonged phase of subclinical infection. Some chronically infected dogs eventually develop disease manifestations of canine monocytic ehrlichiosis, which can include pancytopenia, profound hyperglobulinemia, bleeding diathesis, and renal disease. While tetracycline antimicrobial treatment is very effective for acute disease, chronic manifestations such as pancytopenia may respond poorly, and chronically ill dogs may die despite antimicrobial therapy. Dogs can develop illness many years after initial infection.

On the other hand, E ewingii infection can be persistent but disease seems to be acute, although evidence exists that kidney disease, and especially proteinuria, might be a longer-term consequence of infection. Febrile polyarthritis and neurologic manifestations are described in the weeks after tick transmission. The prevalence of antibodies to E ewingii in endemic regions can be very high, but clinical disease is not nearly as common. It seems that dogs with incidentally discovered antibodies to E ewingii but in apparent good health are unlikely to develop disease directly attributable to infection.
The human pathogen *E chaffeensis* causes a serious mononuclear infection in humans. Experimental infections of dogs have thus far resulted in mild thrombocytopenia but no clinical illness, although natural infections might cause disease signs. Dogs in endemic regions (the same regions endemic for *E ewingii*) are commonly infected and develop potentially cross-reactive antibodies.

**SCREENING TESTS**

There are a handful of infectious agents for which routine screening is common in pet animals (e.g., retroviruses in cats, heartworms in dogs). In general, screening tests should be considered if the results will affect case management. For example, a positive heartworm test would lead to treatment of infection prior to development of heartworm disease with heart failure. Identification of feline immunodeficiency virus infection would lead to alterations in housing and management for the infected cat.

When it comes to screening for *Ehrlichia*, there are pros and cons to consider:

**Pros**
- Informs ectoparasite control practices
- May allow treatment before disease occurs (subclinical phase of *E canis*)
- Provides local regional prevalence information
- Provides sentinel information (human and animal infections)

**Cons**
- May lead to unnecessary treatment with associated costs, potential adverse effects, or possible antimicrobial resistance
- False positives in low-prevalence areas
- Infection that may never cause clinical disease
- Past infection resolved despite antibody detection
- Treatment may not eliminate the potential pathogen (and therefore may not prevent chronic disease)
- Treatment does not prevent reinfection but might provide a false sense of security

**TABLE 1 *Ehrlichia* Species of Clinical Importance**

<table>
<thead>
<tr>
<th></th>
<th><em>Ehrlichia Canis</em></th>
<th><em>Ehrlichia Ewingii</em></th>
<th><em>Ehrlichia Chaffeensis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Important cause of human disease?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Important cause of canine disease?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cell tropism</td>
<td>Mononuclear</td>
<td>Phagocytic</td>
<td>Mononuclear</td>
</tr>
<tr>
<td>Tick vector</td>
<td><em>Rhipicephalus sanguineus</em> (brown dog tick)</td>
<td><em>Amblyomma americanum</em> (lone star tick)</td>
<td><em>Amblyomma americanum</em> (lone star tick)</td>
</tr>
<tr>
<td>Endemic region</td>
<td>All temperate climates worldwide</td>
<td>Southeastern, south-central, and mid-Atlantic U.S. states</td>
<td>Southeastern, south-central, and mid-Atlantic U.S. states</td>
</tr>
<tr>
<td>Chronicity of illness</td>
<td>Acute or chronic</td>
<td>Only acute illness recognized</td>
<td>Acute illness in humans</td>
</tr>
<tr>
<td>Common acute disease manifestation in dogs</td>
<td>Febrile malaise</td>
<td>Febrile malaise, polyarthritis, +/- neurologic signs</td>
<td>Clinical signs not described</td>
</tr>
<tr>
<td>Common chronic disease manifestations in dogs</td>
<td>Bleeding diathesis, pancytopenia, renal disease, neurologic signs, uveitis</td>
<td>Possible renal disease</td>
<td>None recognized</td>
</tr>
</tbody>
</table>
Antigen Versus Antibody Tests
Screening tests must be sensitive so that they do not miss infections. Tests that detect antigen (e.g., most serologic heartworm and feline leukemia virus tests) prove that a pathogen is present in the sample. However, in the case of *Ehrlichia*, serologic antibody tests are the screening method of choice.\(^\text{15}\) Antibody tests detect the host’s response to a pathogen, and antibody formation takes some time (typically 2 to 3 weeks). As a result, antibodies may be absent during acute infection/illness, which is why convalescent titers to demonstrate seroconversion or a 4-fold increase in titer are often required to confirm acute disease (e.g., leptospirosis, Rocky Mountain spotted fever). On the other hand, antibodies may persist after an infection has resolved, or at least after any threat of disease due to infection.\(^\text{16}\) For example, dogs infected with *E ewingii* may remain well or develop acute illness, but chronic illness is not likely even if antibody titers persist.

Antibodies can be cross-reactive, meaning that a positive test result may be due to previous or current infection not with the pathogen of interest but with a related organism (pathogenic or not). As an example, antibodies to *Ehrlichia* species in a dog might result from *E chaffensis* infection that is unlikely to ever have clinical consequences. Furthermore, current commercially available serologic tests cannot differentiate between the *Ehrlichia* species that lead to a positive antibody test result.

Predictive Value
Any test, no matter how good, is subject to both false-positive and false-negative results. These are reflected in the diagnostic sensitivity and specificity of the test. Diagnostic sensitivity refers to the proportion of tests run on infected animals that are truly positive, while diagnostic specificity refers to the proportion of tests run on noninfected animals that are truly negative. To “rule out” a diagnosis, a test with a high sensitivity is desired, while to “rule in” a diagnosis, high specificity is needed. For screening purposes, a test with high sensitivity is preferred over one with high specificity.

In the clinical setting, the positive and negative predictive values of a given test are even more important than its sensitivity and specificity. Positive predictive value is the probability that an animal that tests positive actually has the infection in question, while negative predictive value is the probability that an animal that tests negative is free of infection. While positive predictive value certainly is related to the sensitivity and specificity of the diagnostic assay, it is also related to the prevalence of disease in the population of animals tested: a positive test result in a population with a low prevalence of the tested disease has a greater chance of being a false positive than when the same test is used in a population with a high disease prevalence, even when the test used is very sensitive and specific.

For example, if a diagnostic test has a sensitivity of 95% and a specificity of 90%, the positive predictive value of that test in a population with a 50% pathogen prevalence would be 90%. This means that 1 out of 10 positive results would be a false positive. However, if the same test is used in a population with a 5% pathogen prevalence, the positive predictive value would be 33%, meaning that 2 out of 3 positive results might be false positives.

TREATMENT CONSIDERATIONS
In light of all this information, what are the considerations when a healthy dog tests positive for *Ehrlichia* infection?

Ectoparasite Control
First, a positive *Ehrlichia* screening result should prompt reevaluation of ectoparasite control with the pet owner (Box 1). For owners who have not been using veterinarian-recommended parasiticides because they do not understand the risks of tick bites or the prevalence of ticks in the area, or because they favor “natural,” poorly evaluated, or less reputable products (or their own tick-removing abilities), a positive screening test can be a wake-up call. Not only did their dog have a tick, but that tick infected it with a pathogen. A positive result clearly demonstrates that tick control must be stepped up. Pet owners should also be made aware that prior infection does not prevent future reinfection, and second infections might cause disease even if the initial infection did not.

Test Characteristics
Second, know the test used to screen and what a positive result means.\(^\text{18,19}\) Multiple screening tests exist, and each detects different antibodies with different potential for cross-reactivity. Does the test being used pick up all 3 relevant *Ehrlichia* species or only *E canis*? Additionally, each test has different sensitivity and specificity; you should know not only the
manufacturer-described sensitivity/specificity but also be aware of any comparative studies.

Infection Prevalence
Third, know the prevalence of infection in your area.\textsuperscript{2,14,20} Prevalence does not alter sensitivity or specificity but has a tremendous impact on positive and negative predictive value. The less common actual infection is in a given area, the more likely that a positive test result is a false positive. In some areas, the less pathogenic \textit{Ehrlichia} species are more commonly encountered than the more pathogenic ones. Decisions on “next steps” after a positive result are therefore likely to depend on the relative local prevalence of different \textit{Ehrlichia} species. For instance, a positive result in Missouri is more likely due to \textit{E ewingii} or \textit{E chaffeensis}, while in New Mexico it is more likely due to \textit{E canis}. The Companion Animal Parasite Council website (capcvet.org/maps) is a good source of relevant prevalence information.

Further Testing
Fourth, make sure the “healthy” dog is healthy. Perform a complete blood count (CBC) with blood smear, urinalysis (and, if proteinuria is identified, a urine protein:creatinine ratio), and serum biochemical profile (or at least a renal profile). Findings that support antimicrobial treatment include morulae, thrombocytopenia, anemia, and hyperglobulinemia. Identification of morulae is insensitive but should prompt antimicrobial treatment.\textsuperscript{11,21} Morulae are identified most often in acute rather than chronic infections; therefore, it is uncommon to see them in a healthy dog, but if found in monocytes they suggest \textit{E canis} while if found in phagocytes they suggest \textit{E ewingii} (or \textit{Anaplasma phagocytophilum} infection, which results in identical morulae). If azotemia or proteinuria is present, it is important to consider causes other than ehrlichiosis that might require investigation, but antimicrobial therapy is possibly indicated in these dogs.\textsuperscript{22-24}

**CHOICES FOR HEALTHY DOGS**
If the seropositive dog is truly healthy—that is, it is well per owner report and physical examination and has normal laboratory findings—involve the pet owner in a discussion of the risks and benefits of the 3 options outlined below. There is no “right” decision for these dogs beyond amending the tick control program, because there is no evidence as to the best option. Risks and benefits are informed by individual animal factors as well as prevalence of pathogens in the area.

1. Treat with antimicrobial drugs (doxycycline 10 mg/kg PO q24h for 28 days or minocycline 10 mg/kg PO q12h for 28 days)

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**BOX 1** Tick Control Recommendations for Owners

1. Do not allow dogs to roam, and reduce tick habitat in the yard.
   - Remove leaf litter.
   - Mow your lawn frequently.
   - Clear tall grass and brush around your home.
   - Use a 3-foot-wide barrier of wood chips or gravel between lawns and wooded areas.
   - Discourage wildlife from visiting the yard by installing fencing.
   - Remove hiding places for rodents and ticks by stacking wood neatly in dry areas, keeping yards free of excessive debris, and not leaving food available.

2. If buildings become infested with ticks (especially \textit{Rhipicephalus sanguineus}), engage a professional exterminator.

3. Check pets daily for ticks, especially around the ears and eyes, between the legs and toes, around the tail, and under the collar. Perform tick checks even when using tick prophylaxis, as no prophylaxis is perfectly effective. The transmission time of \textit{Ehrlichia} species has been shown to be faster than some other tick-borne pathogens of concern in dogs (as little as 3 hours of feeding may result in pathogen transmission).\textsuperscript{17}

4. Use appropriate tick prophylaxis for all dogs and cats in the home (keep in mind that many chemicals considered safe for dogs may be toxic for cats).
   - Collars (e.g., imidacloprid/flumethrin, amitraz)
   - Orals (e.g., fluralaner, afoxolaner, lotilaner, sarolaner)
   - Spot-on (e.g., fipronil)
   - Sprays (e.g., fipronil)

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Because many dogs infected with *E canis* might remain healthy and never develop chronic disease, and dogs infected with *E ewingii* or *E chaffeensis* are unlikely to develop chronic disease, simply monitoring the dog may be adequate.

2. Investigate further, either with additional or different serologic tests or with a polymerase chain reaction (PCR) test
3. Adopt a “watch and wait” approach, which includes client education on clinical signs of ehrlichiosis in dogs

**Antibiotic Therapy**

Administering antibiotics has the potential benefit of reducing the risk of development of chronic disease. However, there is evidence that a 28-day course of tetracyclines may not eliminate *Ehrlichia* pathogens.\(^{25}\)

If the organism is not eliminated, there is a real possibility it could proliferate and eventually still lead to chronic disease even after antibiotic treatment. Although tetracyclines are generally safe, they are associated with potential adverse events (most commonly gastrointestinal upset), they might alter the normal microbiome and/or lead to antimicrobial resistance in commensal microbes, and they come at costs of both money and effort by the pet owner.\(^{26,27}\)

Because elimination of the organism is not certain, even dogs treated with antimicrobials should be monitored on at least a yearly basis as with the “watch and wait” approach.

**Further Investigation**

If an owner chooses to investigate further, PCR testing to detect circulating *Ehrlichia* DNA and serologic testing to determine a specific antibody titer or differentiate between the species of *Ehrlichia* are options.\(^{1,21}\) While a positive PCR result would convincingly demonstrate active infection and could reasonably prompt antimicrobial therapy, a negative result does not prove that the dog is not infected, as the number of organisms present in the submitted sample can vary day to day.\(^{28}\) It is well known that PCR results for blood tests can be negative for *E canis* while results for tissue tests are positive.\(^{29}\)

Although serologic titer can be quantified (as opposed to just the “positive or negative” results of screening tests), there is no evidence that a higher titer is more likely than a lower titer to precede disease development. In regions where all 3 species of *Ehrlichia* are recognized (i.e., southeastern, mid-Atlantic, and south-central states), determining which organism is causing antibody production might be useful. *E canis* can cause disease signs long after initial infection while the other species may not; therefore, confirmation that an infection is caused by *E canis* might make antimicrobial therapy a more attractive option than infection by the other species. Consult with your laboratory to determine if they can perform serologic speciation.

**Watch and Wait**

The third option for these healthy animals would be to adopt a watch-and-wait approach. Because many dogs infected with *E canis* might remain healthy and never develop chronic disease, and dogs infected with *E ewingii* or *E chaffeensis* are unlikely to develop chronic disease, simply monitoring the dog may be adequate. Besides educating the owner on possible evidence of disease, the watchful waiting should include yearly repetition of CBC, serum biochemical or renal profile, and urinalysis. As when first evaluating a seropositive dog, abnormal findings on these tests (e.g., morulae, thrombocytopenia, anemia, proteinuria, hyperglobulinemia) would prompt treatment.

**SUMMARY**

Positive screening serologic test results for *Ehrlichia* species exposure in dogs requires veterinarians to make decisions as to next steps, taking into consideration geography and prevalence of pathogens in the area, individual animal factors, and owner wishes. Reevaluation of ectoparasite prevention is always appropriate. Assessment of health via not only history and examination but CBC with blood smear, serum biochemical profile, and urinalysis is also indicated both at the time of screening and on a yearly basis thereafter. Antimicrobial therapy, additional confirmatory diagnostic testing aimed at specific
References


