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Tickborne and other stealth pathogen reproductive concerns
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Abstract
Tickborne and other stealth pathogens may cause illness or persist in seemingly healthy dogs and cats. Question: Might premunitive carrier status in a breeding animal have an impact on reproduction or the next generation? This review considers and compares the geographic distribution, transmission, clinical signs of illness, diagnostic tests for sick animals and for the identification of nonclinical carrier status, treatments, and prevention of anaplasmosis, babesiosis, bartonellosis, borreliosis, cytauxzoonosis, ehrlichiosis, hepatozoonosis, leishmaniasis, hemotropic mycoplasmosis, and rickettsiosis. These diseases are generally considered vector-borne but some may also be acquired vertically (mother to offspring) or horizontally via bites/fights, or by blood product transfusions.

Keywords: Carrier, cytopenia, Lyme, proteinuria, transplacental, vertical

Introduction
Most of the tickborne infectious diseases (TBDs) involve stealth pathogens, which often go undetected in long-term carriers which are nonclinical (asymptomatic) until perhaps coinfections, immunosuppression (by drugs or disease), or stress occurs. Some of the diseases cause illness more often in certain breeds, possibly due to genetic predisposition (eg, Ehrlichiosis¹² in German Shepherds (E. canis) or Lyme nephritis³⁶ in Labrador and Golden Retrievers); life-style (e.g., babesiosis⁷ in Greyhounds [B. canis] or Pit Bull Terriers [B. gibsoni]); or due to vertical transmission (e.g., in babesiosis [as above]⁸⁹ or leishmaniasis¹⁰−¹⁵ in American Foxhounds).

Many questions may arise as reproductive concerns. Here are just the top 10:
1. What types of ticks and TBDs are we talking about, where are they endemic, and what kinds of signs might we see with illness?
2. What diagnostic tests are available for sick dogs? Should breeding dogs be screened for TBDs and which diagnostic tests should be used in those cases?
3. Can these diseases affect fertility?
4. Can these diseases be transmitted venereally or from frozen semen?
5. Should a nonclinical carrier be treated before breeding and can it be completely cleared?
6. Will the stress of pregnancy or lactation cause a carrier to become ill?
7. Can these diseases be transmitted vertically to offspring (in utero or during lactation)?
8. Should the gravid or nursing patient be treated?
9. How do we diagnose these diseases in the very young and should they be treated?
10. How do we best protect breeding dogs and their young offspring from these diseases?

Although we do not have all the answers to all of these questions yet, veterinarians working with breeding animals and their young offspring are wise to be on the lookout for the TBDs in their geographic area, and should also be aware of the TBDs in other areas where animals may have travelled for shows, breeding, or family vacations. They should also consider any history of bites/fights, splenectomy, blood transfusions, and illness in relatives (ancestors, littermates) or in other pets in their environs.

Q1: What types of ticks and TBDs are we talking about, where are they endemic, and what kinds of signs might we see with illness?
There are four major kinds of hard ticks, which are each 3-host ticks, including *Ixodes scapularis* (the deer tick or black-legged tick), *Dermacentor variabilis* (the American dog tick), *Rhipicephalus sanguineus* (the brown dog tick), and *Amblyomma americanum* (the Lone Star tick). Hard ticks usually quest for hosts outdoors (except *R. sanguineus*, which is found in kennels) and are found in geographic...
‘endemic areas’ which may be extended by host migration, including bird migration. There are also soft argasid ticks (Ornithodoros spp) that transmit diseases. Each kind of tick may carry more than one kind of organism, for instance, Ixodes scapularis may carry spirochetes (Borrelia burgdorferi [the agent of Lyme disease], B. miyamotoi and B. davisii [these last two are among the relapsing fever group of Borrelia spp]), two types of rickettsia (Anaplasma phagocytophilum and the Ehrlichia muris–like agent), a protozoan (Babesia microti), bacteria (Bartonella spp), a virus (Powassan or tick–borne encephalitis virus), and possibly more! I. scapularis is found in the northeast, midAtlantic, and upper midwestern United States, where its hosts are usually small mammals, birds, and deer. In western states, I. pacificus can transmit Lyme disease, but it feeds on reptiles, which are not as good reservoirs of the agent.

Tables 1 and 2 show a variety of TBDs, with comparisons of their vectors, targeted cell types, clinical signs, diagnostic tests and whether paired titers may be needed, treatments, and whether the agent is bloodborne.

Lyme disease,3–6 caused by Borrelia burgdorferi, is the most common TBD in the USA. Luckily only about 5% of Lyme-seropositive dogs show illness that is suspected due to the agent. In some areas of New England, 70-90% of healthy dogs are seropositive. Experimentally, Lyme disease induced by the tick model caused high antibody titers but no signs of illness in adult beagle dogs and puppies over six months old. In young (six–12 wk) beagle puppies experimentally infected, after a two to five month incubation, only a self-limiting illness (four days) of fever, anorexia, and arthritis in the leg closest to the tickbites occurred, with possibly a few similar recurrences in the same or different leg every two weeks. Older puppies (13–26 wks) showed milder signs (two days) and fewer recurrences. None of the experimental dogs developed proteinuria. Perhaps less than 2% of Lyme-seropositive dogs show “Lyme nephritis”, a protein-losing nephropathy (PLN) due to immune-complex glomerulonephritis, for which Labrador Retrievers, Golden Retrievers, and perhaps Shetland Sheepdogs appear predisposed genetically. However, even among seropositive retrievers, proteinuria is uncommon.16 Rash, cardiac, or neurologic signs of Lyme disease in dogs are not well-documented. Seropositive cats are even less likely to show any illness. Since Lyme Borreliosis travels by tissue migration and not generally hematogenously, seropositive animals may be used as blood donors. The diagnosis and treatment of PLN is reviewed elsewhere3.17–21

Tables 1 and 2 do not include B. lonestari (from Amblyomma ticks) that causes “Southern tick-associated rash infection” (STARI) in people in southern states, mimicking the rash of Lyme disease22 (it is unknown if this species causes illness in animals) or the tickborne relapsing fever (TBRF) group of Borrelia spp, which may get more attention in the future, including B. miyamotoi and B. davisii (in I. scapularis ticks in Lyme endemic areas) and B. hermsii and B. turicatae (transmitted by soft Ornithodoros ticks, which only feed for 15–90 minutes, in northwestern and southern states, respectively), associated with log cabins and sheds.23–28 The TBRF group of Borrelia spp do circulate hematogenously, cause relapsing fever, myalgia/arthralgia, and neurologic signs in people and possibly illness in dogs/cats.

Anaplasmosis and ehrlichiosis1 (rickettsial infections) are probably next most common after Lyme borreliosis. A. phagocytophilum may be seen alone or as a coinfection in Lyme endemic areas, with similar signs of fever, anorexia, lameness, and possibly thrombocytopenia and other cytopenias.29,30 Coinfected dogs may be more likely to become clinically ill.31 In the upper midwestern states, seropositivity against A. phagocytophilum is just as common as against B. burgdorferi. A. platys, a rickettsial parasite of platelets, is endemic in southern and Gulf states, often with E. canis coinfection. Ehrlichiosis is mostly seen in southcentral and eastern states. Mononuclear forms generally cause cytopenias, especially thrombocytopenia (E. canis and E. chaffeensis).30,32 A newly recognized mononuclear form, E. muris–like, is found in the upper midwest and is probably transmitted by I. scapularis ticks.33,34 E. canis may cause more severe illness (especially in German Shepherds), pancytopenia, bone marrow suppression, hypoalbuminemia, proteinuria, hyperglobulinemia (even perhaps with monoclonal gammopathy, mimicking multiple myeloma), hemorrhage, and neurologic signs. A granulocytic form, E. ewingii,35 is associated with fever, polyarthropathy, and possibly cytopenias, and mimics anaplasmosis and/or Lyme disease.
Rocky Mountain spotted fever (RMSF) due to *Rickettsia rickettsii*, is more common along the eastern seaboard (transmitted by *D. variabilis*) than in the Rocky Mountains (transmitted by *D. andersoni*, the Rocky Mountain wood tick) and in the southwest by *Rhipicephalus* ticks. Rocky Mountain spotted fever may mimic ehrlichiosis in many ways but is more likely to cause vestibular neurologic signs and unlike most of the other TBDs, RMSF is not associated with carrier status, therefore the illness is seen acutely and seasonally, occurring within one to two weeks after the tick bite. In addition to doxycycline, RMSF can be treated with fluoroquinolones.

Bartonellosis, often thought of as a flea-transmitted disease, can also be transmitted by ticks, bites/fights, transfusions, and possibly vertically. There are many species, e.g., *B. henselae* (the agent of cat scratch fever), *B. vinsonii, B. quintana, B. clarridgeiae, B. elizabethae, B. koehlerae, B. washoensis*, etc. Bartonellosis may be a coinfection with Lyme disease, Anaplasmosis, and others. In our area, 7.5% of healthy dogs and 20% of hospitalized dogs were seropositive. Carriers may be nonclinical or have endocarditis, hepatitis, vasculitis, uveitis, neurologic disease, anemia, cytopenias, immune-mediated and potentially other illness (because of coinfections, it can be difficult to know if bartonellosis is the sole cause of signs).

Red blood cell TBDs such as babesiosis and hemotropic mycoplasmosis may mimic immune-mediated hemolytic anemia presentations, e.g., with regenerative anemia, spherocytes, autoagglutination, Coombs’ positive test results, icterus, and splenomegaly. Babesiosis may cause intravascular as well as extravascular hemolysis, with hemoglobinemia and hemoglobinuria, as well as the bilirubinemia and bilirubinuria seen with extravascular hemolysis, whereas hemotropic mycoplasmosis (previously called hemobartonellosis) is associated with only extravascular hemolysis. Large piroplasms include *B. canis* (*B. canis canis, B. canis vogeli, B. canis rossi*, and novel as yet unnamed varieties). Smaller piroplasms include *B. gibsoni, B. conradae, and B. microti*-like (also called *Theileria annae*), with possible PLN and thrombocytopenia syndromes. Babesiosis is transmitted by *Rhipicephalus* all over the US, but especially seen in Greyhounds (*B. canis*) from racetracks or kennels, and in American Pit Bull and Staffordshire terriers and Tosa Inu breeds (*B. gibsoni*) possibly also transmitted by bites/fights and from mother to offspring. Mycoplasmosis may be transmitted by fleas as well as bites/fights. Mycoplasmosis due to *M. haemofelis* is more pathogenic than *M. haemominutum* in cats, and *M. haemocanis* more so than *M. hematoparvum* in dogs. Cats that are ill with mycoplasmosis should be tested for comorbidities/coinfections, e.g., FeLV/FIV. Dogs ill with mycoplasmosis may have comorbid disease, immunosuppression, splenic disease or a history of splenectomy. *Cyt luxzoom felis*, a feline red blood cell protozoan, is transmitted by *Amblyomma* ticks, and seen in cats mostly in the southern states, but positive reservoir bobcats have been found as far north as Pennsylvania. This hemolytic disease has been associated with vascular blockade and high mortality, however up to 15.5% of healthy domestic cats in Arkansas may be carriers, followed by a 12.9% carrier rate in Missouri and 3.4% in Oklahoma.

Hepatozoonosis is due to *H. americanum* and/or the less pathogenic (European) *H. canis* in the southeastern US and is unique in that dogs become infected by eating the tick or raw encysted meat. Chronic muscle wasting and protein-losing nephropathy may be seen but a hallmark of *H. americanum* is periosteal proliferation seen radiographically. *H. felis* may be a problem in cats travelling to other continents.

Leishmaniasis is not common in the US because of the absence of the sandfly vector, however American Foxhounds, Corsicas, Spinones, and Neapolitan Mastiffs may be predisposed because of transfer of the infection vertically (mother to offspring) and possibly by bites/fights. Dogs of other breeds have been infected inadvertently via blood transfusions from carriers. The disease has travelled to different areas of the US with infected dogs. The disease is associated with chronic wasting, glomerulonephritis, fever, enlarged reticuloendothelial system organs, bone marrow damage, PLN, ocular, and skin changes.

Q2: What diagnostic tests are available for sick dogs? Should breeding dogs be screened for TBDs and which diagnostic tests should be used in those cases?
Since so many of the TBDs mimic each other, e.g., by causing proteinuria, cytopenias, and/or polyarthritis, it is important to be aware of the differential diagnoses among the TBDs as well as other differentials that can cause those signs (infectious, inflammatory, immune-mediated, neoplastic, toxic, traumatic, degenerative, genetic, etc). It is essential to keep an open mind since so many animals are nonclinical carriers (for instance, in some Lyme endemic areas, 70-90% of healthy dogs are seropositive) and the finding of a positive test result may be coincidental and not proof of the cause of illness. One study showed that 40% of dogs diagnosed with Lyme disease actually had other causes for their signs and were eventually realized to be misdiagnosed.53 Other diseases may present during an acute stage, before seroconversion (e.g., anaplasmosis, ehrlichiosis, RMSF, leptospirosis) so paired or convalescent testing is required. Doxycycline (or minocycline) is often given when TBDs are suspected, to treat possible susceptible coinfections (spirochetes, rickettsials). But a favorable response to treatment is still not proof of cause since improvement may be coincidental over time, doxycycline (or minocycline) treats a variety of (undetected) coinfections, and the tetracycline family has antiinflammatory and antiarthritic properties.

When dogs are sick with signs of TBDs, veterinarians often wonder which tests are better, tests for antigen (cytology by blood smear, joint tap, lymph node or bone marrow aspirate as the agent requires, culture, or PCR) or tests for antibodies (IFA, ELISA, WB, etc.)? For sick animals, usually every piece of the puzzle is helpful in different ways under different circumstances, and you may need to submit multiple different types of tests on an individual.54 Tests for antigen may be most helpful during acute stages of illness, before seroconversion and before starting treatment (to avoid a ‘false’ negative result). Consider PCR testing of whole blood for blood-borne agents, but realize that the small aliquot of blood sampled may be negative, especially if even one dose of treatment has been given, and that false positive PCR test results may occur due to contamination at the laboratory (controls are essential). For antibody tests, seroconversion may not occur until two to three weeks after signs of illness present, therefore paired titers may be necessary. Consider cross-reactive antibodies, for instance, other spotted fever group rickettsial infections cross-react with serologic tests for RMSF. Some Lyme tests (OspA and OspC antibodies) may be seen in both naturally exposed and vaccinated animals. Consider that for some diseases which do not present until chronic stages, the animal should have seroconverted by the time it presents with clinical signs due to that disease (Lyme disease, leishmaniasis). If the signs of illness are chronic, testing for RMSF is likely unnecessary.

A positive test result for any TBD is a marker for tick and wildlife exposure, and coinfections with other TBDs and other infectious agents should be considered (eg, leptospirosis may mimic Lyme nephritis).55 As another example, a dog may be found to be Lyme-seropositive but its illness may be due to Anaplasmosis or RMSF presenting during the acute phase, before seroconversion, or due to babesiosis, for which separate testing is required. See Tables 1 and 2 for a listing of some TBDs as well as leptospirosis and brucellosis, which are included for comparisons.

Since *Borrelia burgdorferi* does not circulate hematogenously, and because there are few organisms to be found in tissue samples and they are difficult to grow in vitro in the laboratory, antibody tests are preferred. Table 3 shows the variety of serologic tests available for antibodies against Lyme disease. Older tests (whole cell IFA, ELISA, IgM/IgG, or Western blot), while no longer as helpful for Lyme diagnosis because of cross-reactive antibodies with other spirochetal infections and vaccinal antibodies, may be interesting to study now that emerging *Borrelia* spp of the TBRF group may become a problem (TBRF antibodies do not cross-react on C6 peptide tests).

The newer SNAP-4DxPlus (IDEXX) and AccuPlex4 (Antech) are the most common screening tests done for sick and healthy animals. Websites are available that show the prevalence of positive test results (www.dogsandticks.com/diseases_in_your_area.php and www.capcvet.org/parasite-prevalence-maps/) down to the county level. The canine SNAP-3Dx, -4Dx and -4DxPlus (IDEXX) tests do not use species specific reagents and may be used on cats, horses, and other species, off label. Lyme antibodies against the C6 peptide of the VlsE antigen are specific for natural exposure antibodies. Although the height of the quantitative titer does not predict illness, the C6Quant (IDEXX) level has been shown to wane three to six months after treatment, while the other tests for antibodies have not been shown to wane with treatment (eg, ospF). Comparisons of pre- and three to six month post-treatment C6Quant are
helpful for trend, and to compare in the future if signs of illness occur, to see if there is any reason to suspect Lyme disease as cause and whether retreatment is indicated. While some tests purport to show whether the Lyme titer represents acute or chronic infection, they may merely indicate when the dog was last exposed but not when it was first exposed, and also there is no evidence that whether the infection is acute or chronic is clinically relevant. The use of IgG and IgM titers is not helpful in dogs since the incubation is two to five months before signs, and the dogs would not be presented during a time when they were IgM positive and IgG negative.

Healthy breeding dogs are often screened for brucellosis, but should they be routinely screened for TBDs? This author thinks so, certainly if they are ill with suggestive signs, but also if they are nonclinical but live or have travelled to endemic areas, or a predisposed breed, or if there have been other possible exposures (living with an affected animal, bites/fights, history of transfusions, splenectomy, etc). Using screening tests help to identify dogs at risk for proteinuria or other stealth pathogen consequences, sentinels for public health hazards, and to show if the use of tick control is adequate. The most commonly used screening tests are the IDEXX in-house kits (SNAP-3Dx, SNAP-4Dx or SNAP-4DxPlus) and the AccuPlex4 (Antech Reference Laboratories). These are qualitative tests for the presence of heartworm antigen and for antibodies against Lyme disease, anaplasmosis, and ehrlichiosis. There are differences, e.g., the E. canis test on the IDEXX tests may pick up cross-reacting antibodies to E. chaffeensis and possibly the E. muris-like agent, the A. phagocytophilum test may pick up A. platys antibodies, and there is also a specific test on the SNAP-4DxPlus test for antibodies to E. ewingii, while the AccuPlex4 may not pick up these antibodies. The AccuPlex4 claims to show antibodies 12 days earlier against E. canis and one week earlier against Lyme and A. phagocytophilum than the SNAP-4Dx tests, but the SNAP-4DxPlus test was found to be more sensitive and specific for Lyme and Anaplasma antibodies than the AccuPlex4 in a recent study.

Comprehensive tick panels including PCR and serologic tests for the more common TBDs are available, for instance at the Vector Borne Disease Diagnostic Laboratory (VBDDL, at North Carolina State University, Raleigh, NC), IDEXX Laboratories, and Antech Diagnostics. Galaxy Diagnostics (Durham, NC) does Bartonella BAPGM enrichment blood culture/PCR testing. The National Veterinary Laboratory, Inc (Franklin Lakes, NJ) does the Bartonella Western Blot antibody test (the ‘FeBart’ test is a species specific test but canine reagents can be used for dog samples). Less common tests and the laboratories that do them have been reviewed elsewhere.

Q3: Can these diseases affect fertility?

There is no evidence that nonclinical carriers are less fertile. There is some evidence that coinfected dogs are more likely to become ill than dogs carrying only one organism, possibly due to immune system modifications, which potentially could affect general health including fertility.

Q4: Can these diseases be transmitted venereally or from frozen semen?

The TBDs are generally not thought of as venereal diseases. Besides arthropod vectors, the bloodborne diseases may be transmitted by blood or blood product transfusions, contaminated needles or surgical equipment, bites and fights, ingestion of blood and possibly saliva (Bartonella and Mycoplasma spp). Since blood may be present in semen or in the vagina, it is theoretically possible that transmission during breeding could occur. Although the agent of Lyme disease may be found rarely by PCR in blood, urine, or semen, viable organisms are very rarely present. Control dogs remained Lyme-seronegative even after being housed with seropositive dogs for more than a year. The agent of visceral leishmaniasis, L. chagasi, has a tropism for the male genitalia and venereal transmission, as the organism is shed intermittently in the semen of infected dogs, causing infection in breeding bitches in experimental settings without the natural vector present.

Q5: Should a nonclinical carrier be treated before breeding and can it be completely cleared?

Treating nonclinical, nonproteinuric dogs that are seropositive for Lyme, Anaplasma, or Ehrlichia spp is not advocated. It may not be possible to truly clear a carrier dog with treatment anyway. For
instance, during treatment of anaplasmosis with doxycycline, the PCR test on the blood will be negative, but then positive again after treatment, or when challenged with steroids.70,71 However, I would try to treat babesiosis in a carrier, to try to prevent illness during the stress of pregnancy, and vertical transmission to the offspring, although babesiosis is not always able to be cleared, especially in splenectomized animals.42 Treatment may not be able to clear all animals of bartonellosis, cyauxzoonosis, mycoplasmosis, and Lyme disease.39,44,47,72 Treatment may decrease antigenic load and produce a nonclinical premunitive carrier status, but these should not be used as blood donors (if the organism is bloodborne). In some cases of splenectomized dogs with babesiosis, if clearance with other antiprotozoal treatments fails, longterm clindamycin may be used. For hepatozoonosis, treatment is always longterm, in order to deal with organisms as they are released from muscle cysts. Similarly, treatment for leishmaniasis is longterm and may not be able to eradicate the organism.73

Q6: Will the stress of pregnancy or lactation cause a carrier to become ill?

It may be argued that a carrier may come out of the nonclinical premunitive state and become ill during the stress of pregnancy, therefore treatment may be warranted to try to decrease antigen load and perhaps decrease the risk for illness or transmission during the stress of breeding, pregnancy, or lactation; however, there are no supportive studies to show treatment is indicated or helpful in this regard and the animal may not be cleared.

Q7: Can these diseases be transmitted vertically to offspring (in utero or during lactation)?

There is evidence that babesiosis and leishmaniasis are transmitted vertically,7-15,74 and perhaps TBRF.75 There is evidence for vertical transmission of H. canis and H. felis, but not of H. americanum.39,51 Although there is evidence for transplacental transmission of anaplasmosis in humans and cattle, there is not for dogs.1,76 Lyme disease is probably not transmitted vertically.66,77 Nor was Mycoplasmosis proven to be (without the presence of fleas).38

Q8: Should the gravid or nursing patient be treated?

If the gravid or nursing patient is clinically ill, it will need to be treated. In the past, veterinarians were worried about the use of doxycycline and the effects on the young. It appears that doxycycline is not teratogenic,78 nor does it bind to calcium as much as tetracycline, therefore discoloration of the teeth is not as much a concern.79

If the positive animal is not ill but just suspected (or proven) to be a carrier, consider not treating, especially if there is no reported vertical transmission for the agent. Check for occult proteinuria, CBC, and/or biochemical changes that are associated with TBDs. The pregnancy and offspring need to be monitored carefully.

Q9: How do we diagnose these diseases in the very young and should they be treated?

Since antibodies from the mother are passively bestowed to offspring transplacently during the last trimester and in the colostrum,20 serologic tests alone are not diagnostic for infection in the very young. Although an experimental model utilizing intradermal injections of B. burgdorferi in dogs caused infection in puppies,81 a more natural tick model66 showed that there was no transplacental transmission of Lyme disease in pups, that they were not ill when followed for five months and their maternal antibodies waned by four weeks. The in-house IDEXX SNAP-4Dx test was used on puppies from a Lyme-seropositive dam in the field, showing positive results in the pups at seven days of age, but their C6Quant results were ≤10 on day 18 of life (the dam’s C6Quant result was 112); these puppies were not treated, and showed no signs of illness.82 These reports show no evidence of transplacental transmission of Lyme disease in the tick experimental model of Lyme disease nor in the field, and that passive (maternally derived) antibodies declined within the first few weeks of life.

For other TBDs, when appropriate, a search for the organism by cytology or for its DNA by PCR testing is preferable to prove infection in young puppies, to avoid confusion with material antibodies on
serologic tests. If only serology is available, passive immunity will wane over time, whereas active infection titers will stay stable or trend up over time.

If puppies are ill, they should be treated. Lyme disease can be treated with doxycycline or amoxicillin, but anaplasmosis and ehrlichiosis need to be treated with doxycycline. Although tetracycline may discolor the teeth and should not be given with milk because of calcium binding, doxycycline does not, so it can be used safely in the young. Rocky Mountain spotted fever may be treated with doxycycline or fluoroquinolones, and of those, I would probably choose doxycycline in the young rather than possibly causing cartilage damage with fluoroquinolones. Doxycycline may cause esophagitis and should be given in liquid form, with care to ‘wash’ it into the stomach by water, milk, or food following dosing.

Q10: How do we best protect breeding dogs and their young offspring from these diseases?

While specialists still debate the pros and cons of using Lyme vaccines, there is strong consensus that tick control is most important, because there are many other TBDs in Lyme endemic areas for which there are no vaccines available. Landscaping advice helps to keep pets out of brush where outdoor ticks quest, and kennels should be monitored and treated to avoid *Rhipicephalus* infestations. There are many types of products available which work very well on individuals, including amitraz and permethrin collars (put on tightly enough to have contact with skin, not just fur), topical fipronil and permethrins, and the new oral (chewable) isoxazoline products, which bind specifically to the GABA-gated chloride channel which exists in insects and ticks but not in their hosts. Products which kill the tick before or very soon after tick attachment are preferred, since many TBDs can be transmitted much faster than the two to four days of tick attachment required for the transmission of Lyme or Babesia spp. Permethrins (except for the Seresto collar) are toxic for cats. For dogs that swim or get bathed often, the chewable products may be ideal. See Table 4 for a comparison of tick control products.

Conscientious owners will check their pets every day for ticks and remove them with tweezers or a tick removal device, grasping the tick close to its attachment on the skin, pulling slowly but steadily. Ticks should not be covered with petroleum jelly, burned, or crushed within bare fingers (hemolymph can be infective through cracked cuticles). Tick types may be identified by checking for *Ixodes* ticks’ anal groove (looks like a frown), or by images on-line. In Lyme endemic areas, if a person pulls of an engorged *Ixodes* tick, it is recommended to take one days’ dose of doxycycline within 72 hours, to prevent Lyme disease. No such study has been done in dogs regarding prevention of Lyme or other TBDs that are sensitive to doxycycline.

Other suggestions for prevention include planning for travel to endemic areas with tick control, screening donors before giving transfusions (or transplantation), and having a suspicion regarding TBDs when working with predisposed breeds or animals with a history of bites/fights with those breeds.
Table 1. Some TBDs, ticks, infected cell types, diagnostic tests, treatments, etc.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type of Infected Cell</th>
<th>Major Vector</th>
<th>Tests Beyond Cytology</th>
<th>Need Paired Tests</th>
<th>Bite or Bloodborne Treatment</th>
<th>Status</th>
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<td>Granulocyte</td>
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<td>Platelet</td>
<td>Rhipi ELISA, PCR</td>
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<td>Endothelial cells, Epi-rbc, Macrophages</td>
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<td>X</td>
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<td>Extracellular near fibroblasts</td>
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<td>Ec</td>
<td>Ric</td>
<td>Monocytic wbc</td>
<td>Rhipi ELISA, IFA, PCR</td>
<td>X</td>
<td>X</td>
<td>D</td>
</tr>
<tr>
<td>Ech</td>
<td>Ric</td>
<td>Monocytic wbc</td>
<td>Ambly Derma ELISA, PCR</td>
<td>X</td>
<td>X</td>
<td>D</td>
</tr>
<tr>
<td>Ew</td>
<td>Ric</td>
<td>Granulocyte</td>
<td>Ambly PCR</td>
<td>X</td>
<td>X</td>
<td>D</td>
</tr>
<tr>
<td>Hep</td>
<td>Prot</td>
<td>Myocyte, Lymphoid, Liver, Wbc</td>
<td>Ambly (eating tick, raw meat) PCR Muscle biopsy</td>
<td>No</td>
<td>SPC</td>
<td>X</td>
</tr>
<tr>
<td>Lei*</td>
<td>Prot</td>
<td>Extracellular Macrophages</td>
<td>Sandfly, Vertical IFA, PCR</td>
<td>No</td>
<td>X</td>
<td>PA X</td>
</tr>
<tr>
<td>Lep*</td>
<td>Spir</td>
<td>Extracellular</td>
<td>Urine MAT, PCR ELISA</td>
<td>X</td>
<td>Rare</td>
<td>D (A) X</td>
</tr>
<tr>
<td>Myc</td>
<td>Bac</td>
<td>Epi-rbc</td>
<td>Fleas, Ticks PCR, ELISA (future)</td>
<td>X</td>
<td>DF</td>
<td>X</td>
</tr>
<tr>
<td>Rr</td>
<td>Ric</td>
<td>Endothelial cells</td>
<td>Derma Rhipi, Ambly IFA, DFA</td>
<td>X</td>
<td>Rare</td>
<td>D F No</td>
</tr>
</tbody>
</table>

*Although not TBDs, Bru, Lei, and Lep are included for comparisons


See Abbreviations following Table 2 below.
Table 2. Some TBDs and the clinicopathologic changes they can cause

<table>
<thead>
<tr>
<th>Lameness</th>
<th>UPC or ↑BUN</th>
<th>Vasculitis or Epistaxis</th>
<th>Oculoneural Signs</th>
<th>RCC ↓</th>
<th>WBC ↓</th>
<th>Platelets ↓</th>
<th>Albumin ↓</th>
<th>Globulin ↑</th>
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</thead>
<tbody>
<tr>
<td>Ap</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ay</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Bar</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Bb</td>
<td>X</td>
<td>X</td>
<td>?</td>
<td>Rare</td>
<td></td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Be</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Varied</td>
<td>X</td>
<td>X</td>
<td>?</td>
</tr>
<tr>
<td>Bg</td>
<td>X</td>
<td></td>
<td>X</td>
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<td>X</td>
<td>?</td>
<td>?</td>
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<td></td>
<td></td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Cyt</td>
<td></td>
<td></td>
<td>X</td>
<td>Varied</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ec</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hep</td>
<td>Muscle</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>Up</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lei</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Lep</td>
<td>Muscle</td>
<td>Tubular</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Varied</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Myc</td>
<td>?</td>
<td>?</td>
<td>X</td>
<td>X</td>
<td>?</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rr</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Although not TBDs, Bru, Lei, and Lep are included for comparisons*


See Abbreviations following Table 2 below.
Abbreviations for tables 1-2

A – Amoxicillin
Ambly – Amblyomma
Ap – Anaplasma phagocytophilum
Ay – Anaplasma platys
Bac - bacterial
Bar – Bartonella spp
Bb – Borrelia burgdorferi (Lyme disease)
Be – Babesia canis, rossi, vogeli, large B.
Bg – Babesia gibsoni, conradae, small B.
Bm – Babesia microti-like
Bru – Brucella canis
C6** – C6 peptide antigen in SNAP 3Dx, SNAP-4Dx, SNAP-4DxPLUS or Lyme Quant C6 (IDEXX); *or other Lyme antibody tests: AccuPlex4 (ospA, ospC, ospF, p39, SLP), Abaxis (VlsE, flagellin, ospC), Multiplex4 (ospA,ospC,ospF); IFA; WB; see Table 3 for comparisons
Clin – Clindamycin
Cyt – Cytauxzoon felis
D – Doxycycline
Derma - Dermacentor
E – Erythromycin
Ec – Ehrlichia canis
Ech – Ehrlichia chaffeensis
Ew – Ehrlichia ewingii
F – Fluoroquinolones
Hep – Hepatazoon americanum
IFA – indirect fluorescent antibody
Im – Imidocarb
Lei – Leishmaniasis
Lep – Leptospirosis
MAT – Microagglutination test
MD – Minocycline and dihydrostreptomycin
Myc – hemotropic Mycoplasma spp
PA – Pentostam (sodium stibogluconate), amphotericin B, allopurinol
PLN – protein-losing nephropathy
Proto - protozoa
Q – Atovaquone
R - Rifampin
Rhipi – Rhipicephalus
Ric - rickettsial
Rr – Rickettsia rickettsii (Rocky Mountain Spotted Fever, RMSF)
RSAT – Rapid slide agglutination
Rx – Treatment
SPC - Sulfas, pyrimethamine and clindamycin; decoquinate
Spir - spirochete
UPC – Urine protein/creatinine ratio
WB – Western blot
X - Yes
Z – Azithromycin (Zithromax)
Table 3. Lyme antibody tests available

<table>
<thead>
<tr>
<th></th>
<th>New</th>
<th>Exposure Antibody</th>
<th>Differentiates Vaccinal vs. Natural Exposure</th>
<th>Qualitative</th>
<th>Quantitative</th>
<th>Bedside</th>
<th>Differentiates Acute vs. Chronic Infection</th>
<th>Heartworm</th>
<th>Anaplasma</th>
<th>Ehrlichia</th>
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</thead>
<tbody>
<tr>
<td>Whole cell IFA or ELISA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM/IgG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>Possibly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNAP-4DxPlus (IDEXX)</td>
<td>X</td>
<td>Yes, VlsE (C6)</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C6Quant</td>
<td>X</td>
<td>Yes, VlsE (C6)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VetScan (Abaxis)</td>
<td>X</td>
<td>VlsE, OspC,* Flagellin</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>AccuPlex4 (Antech)</td>
<td>X</td>
<td>OspA, OspC,* OspF, p39, SLP</td>
<td></td>
<td>X</td>
<td>Possibly</td>
<td></td>
<td>X</td>
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<td></td>
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<tr>
<td>Multiplex (Cornell)</td>
<td>X</td>
<td>OspA, OspC,* OspF</td>
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<td>X</td>
<td></td>
<td></td>
<td>Possibly</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OspA and OspC antibodies may be seen at times in naturally exposed and vaccinated dogs.

Antibodies to VlsE (C6) have only been seen due to natural exposure or infection, and have been shown to wane within several months after treatment.

Antibodies to OspA are usually due to vaccination, but can sometimes be seen in non-vaccinates.

Antibodies to OspC are usually due to natural exposure, but they can also be induced by the newer Lyme vaccines. OspC antibodies rise 2-3 weeks after infection and wane naturally (even without treatment) after 3-5 months, unless there is continued exposure.

Antibodies to OspF rise 6-8 weeks after natural exposure, and have not been shown to wane with treatment. See Reference 4 for a further discussion about Lyme Osp antigens.

Antibodies to flagellin may cross-react with other spirochetal/bacterial flagellins.
Table 4. Comparison of some tick control products

<table>
<thead>
<tr>
<th></th>
<th>T, F</th>
<th>Swim</th>
<th>Cats</th>
<th>Prevents Attachment</th>
<th>Age, BW</th>
<th>Pregnancy Lactation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topicals</strong></td>
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<td></td>
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<tr>
<td>Fipronil</td>
<td>T, F</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>≥8 wk</td>
<td>Consult vet</td>
<td>Monthly</td>
</tr>
<tr>
<td>Frontline</td>
<td>T, F</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>≥8 wk</td>
<td>Consult vet</td>
<td>Monthly</td>
</tr>
<tr>
<td>Permethrins</td>
<td>T, F, M</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>≥8 wk, 4#</td>
<td>Consult vet</td>
<td>Monthly</td>
</tr>
<tr>
<td>Activyl T+</td>
<td>T, F, M</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>≥7 wk, 4#</td>
<td>Consult vet</td>
<td>Monthly</td>
</tr>
<tr>
<td>Advantix II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Parastar+</td>
<td></td>
<td></td>
<td></td>
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<td>Vectra 3D</td>
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</tr>
<tr>
<td>Revolution</td>
<td></td>
<td></td>
<td></td>
<td>Does not kill <em>Ixodes</em>, therefore Revolution is not recommended for tick control</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Collars</strong></td>
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<tr>
<td>Amitraz</td>
<td>T only</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>≥12 wk</td>
<td>Consult vet</td>
<td>2-3 months</td>
</tr>
<tr>
<td>Preventic</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Permethrins</td>
<td>T, F, M</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>≥12 wk</td>
<td>Consult vet</td>
<td>6 months (2-3 wk lag) 8 months</td>
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<td><strong>Chewables</strong></td>
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<td></td>
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</tr>
<tr>
<td>Isoxazolines</td>
<td>T, F</td>
<td>Yes</td>
<td>Not yet</td>
<td>No but relatively fast kill</td>
<td>≥8 wk, 4#</td>
<td>Consult vet</td>
<td>1 month 3 months; but 2 months for <em>Amblyomma</em></td>
</tr>
<tr>
<td>NexGard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bravecto</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

BW: body weight; F: fleas; M: mosquitos; T: ticks; wk: weeks; #: pounds
*Products, ingredients, and manufacturers:
Frontline Plus (fipronil, S-methoprene; Merial Limited, Duluth, GA 30096)
Activyl Tick Plus (indoxacarb, permethrin; Merck Animal Health, Intervet Inc, Roseland, NJ 07068)
K9 Advantix II (imidacloprid, permethrin, pyriproxyfen; Bayer Healthcare LLC, Animal Health Division, Shawnee Mission, KS 66201)
Parastar Plus for Dogs (fipronil, cyphenothrin; Novartis Animal Health US, Inc, Greensboro NC 27408)
Vectra 3D (dinitofuran, permethrin, pyriproxyfen; CEVA US, Lenexa, KS 66215)
Revolution (does not kill *Ixodes*; selamectin; Zoetis Inc, Kalamazoo, MI 49007)
Preventic collar (amitraz; Virbac Corporation, Fort Worth, TX 76137)
Scalibor Protector Band (deltamethrin; Merck Animal Health, Intervet Inc, Roseland, NJ 07068)
Seresto (flumethrin, imidoclopramid; Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, KS 66201)
NexGard (afoxolaner; Frontline Vet Labs, Division of Merial Limited, Athens, GA 30601)
Bravecto (fluralaner; Merck Animal Health, Intervet Inc, Summit, NJ 07901)

References


