

THE CONTINUING THREAT OF LEPTOSPIROSIS

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Abstract

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Leptospirosis is a zoonosis found in more than 150 mammalian species, and therefore the risk of this disease to dogs or cats must be dependent on the prevalence of leptospirosis in these species and subsequent environmental exposure risk to dogs. The incidence of canine leptospirosis in the US declined in the 1980s and early 1990s, and interestingly so did human leptospirosis such that CDC removed leptospirosis from its list of nationally notifiable disease (in people) in 1994. Increasing incidence of human leptospirosis however has resulted in CDC making it a notifiable disease again in 2014.

Which serovars are important? The veterinary literature from the 1950s and 60s documented serosurveys of stray unvaccinated dogs in the US, and antibodies against *Leptospira* serovars Canicola and Icterohaemorrhagiae were most common in these dogs. Maintenance hosts for these two serovars are dogs and rats/rodents, respectively. Vaccines were therefore developed in the 1960s to protect dogs against these two serovars. From the mid-1970s to early 1990s, there were few published reports in peer-reviewed literature of canine leptospirosis in the US. This may have been due to reduced infection in reservoir hosts or due to the effectiveness of the bivalent (Canicola and Icterohaemorrhagiae) bacterin. The bacterin was typically marketed as the liquid component of a multivalent canine vaccine. Vaccine-associated adverse events were

sometimes attributed to this bacterin, and post-vaccinal antibody concentrations were reported to decline after 3-6 months, thus leading to questions of the efficacy of this bacterin. Nevertheless, no apparent resurgence of these 2 serovars appeared.

Through the 1990s, case series reports of canine leptospirosis began to document (usually based on serology) infections caused by nonvaccinal serovars. In 1991, Nielsen in Indiana reported 2 leptospirosis cases caused by serovar Bratislava. In 1992, clinicians in Massachusetts reported the canine leptospirosis cases from 1985-1989 in their hospital were predominantly due to serovars Pomona and Grippotyphosa. In 1996, serovar Grippotyphosa was also reported from 11 dogs with acute renal failure in Georgia. The same year, serovars Pomona and Grippotyphosa were reported to cause canine disease in New Jersey and serovars Pomona, Autumnalis, and Grippotyphosa were incriminated in Michigan. Two years later, researchers in New York would report the same 2 serovars as New Jersey, and in 2000 researchers in Davis, CA, would report a predominance of serovars Pomona and Bratislava in their canine leptospirosis cases from 1990-98. They noted that the majority of cases were identified in the last 3 years of their study.

Thus, in the face of possible protection against serovars Canicola and Icterohaemorrhagiae, clinical cases were increasingly attributed to serovars Pomona, Grippotyphosa, Bratislava, and Autumnalis. Serovars Pomona and Grippotyphosa have been recognized pathogens in livestock (cattle and pigs) although until the 1990s they were not pathogens of concern to dogs. They now appear to be established within reservoir wildlife species. The other two serovars (Bratislava and Autumnalis) are documented pathogens on other continents. Bratislava has been associated with clinical disease in pigs (in the US and Europe) and in horses (in Europe), but Autumnalis has not

been isolated from livestock or companion animals in the US. At this time, positive titers to Autumnalis are most likely a cross-reaction from another serovar.

Serovar Icterohaemorrhagiae does remain a threat to many dogs from mice and rats. When sanitary conditions are marginal or house structures allow, rodents in homes can still transmit leptospirosis to dogs who don't go outside! Furthermore as many homes now have backyard poultry (estimated to be >10M homes in the US) the presence of poultry, feed, and litter attract and increase rodent populations and the threat of leptospirosis to dogs.

Clinical signs in dogs are usually attributable to localization of infection to the renal, hepatic, or vascular system. Clinical findings can be quite varied in severity, ranging from acute oliguric renal failure, renal and hepatic disease, fever of unknown origin (FUO), or even no clinical signs (asymptomatic). A general classification of the frequency of organ involvement in canine leptospirosis, based on clinical and diagnostic findings, is: renal only: 30-50%, renal and hepatic: 25-35%, hepatic only: 10-20%, and other (uveitis, myalgia, FUO): 5-10%. Hepatic disease is typically presented as cholangiohepatitis, but several cases of chronic granulomatous hepatitis without renal involvement have also been reported (JVIM 2019). A published report also documented fatal septicemia-like disease in dogs less than 1 year old; these dogs died before a positive-MAT response but were positive for *Leptospira* on special stains of kidney tissue. Some serovars may be more likely to cause disease in certain organs, but there is not consistent evidence to support this perception. Although normally responsive to antibiotic treatment, death can still occur despite treatment (estimated mortality of 15-20% in leptospirosis cases seen at university teaching hospitals).

Determination of the infective serovar and a clinical diagnosis is hindered by lack of a sensitive, specific, low-cost, rapid and widely available diagnostic test for leptospirosis. Most cases of leptospirosis are diagnosed by serology, and the reference method is the microscopic agglutination test (MAT). The MAT is difficult to standardize and requires live organisms for antigens. Cross-agglutination is also common. Despite these drawbacks, the MAT is still the diagnostic norm for many laboratories. Clinicians must presume that the serovar with the greatest antibody titer is the infective serovar, although paradoxical reactions to un-infective serovars have been noted. This is believed to occur most commonly early in infection, due to a non-specific IgM response; the MAT primarily measures IgM rather than IgG. Likewise, clinicians are in a quandary when 2 serovars have equal titers as dual infection is probably unlikely. The use of paired sera (2-4 weeks apart) is often required to confirm the diagnosis and clarify the infective serovar. Problematic however is the capability of leptospiral serovars to alter their outer membrane proteins. This is done in the natural host environment in order to reduce the host immune response to the invader. This transformational ability in laboratory-maintained serovars also could reduce the MAT correlation between laboratories and compared to the infective serovar.

Newer antibody-directed tests have been developed, including ELISA, immunoblot assay, a dipstick method, and a lateral flow assay. Most of these are semi-quantitative tests using a color-change indicator for detecting a titer. These newer tests generally have higher sensitivity in detecting IgM in the first week of infection, but probably no difference by day 14. Advantage to the newer tests compared to MAT may be lower cost, more rapid test results, and improved

sensitivity early in infection; the disadvantages may include no numerical titer, no indication of infective serovar, and an increased risk of false-positive test results due to previous *Leptospira* exposures from environment or recent vaccination.

PCR of urine and/or blood is also used to diagnose leptospirosis before antibiotic administration (early in infection or hospitalization!), but its use and impact have raised new questions.

Although PCR is increasingly available through many laboratories, controlled studies have not defined the correlation between PCR and MAT, using a true “gold standard” in a large number of cases. One limitation of PCR-based diagnosis is the inability of most PCR assays to identify the infecting serovar. While this may not be important for individual patient management, serovar identify has important epidemiological and public health value. Not all PCR tests are performed with the same methodology, and sensitivity and specificity may vary. Generally PCR tests are highly sensitive. False negatives are considered uncommon, but can occur with low/zero levels of leptospiruria or leptospiremia. Certain methodologies however may be more prone to reductions in specificity, causing false positive test results. A comparison study of two PCR methods reported there were 0% false-positives in one method but the same samples had 13% false-positives via the other method. PCR positive results however do not necessarily mean there is viable organism, thus you can get positive PCR results from dead leptospires shed when the dog is receiving antibiotics.

Serological evidence in the US clearly supports the use of 4-serovar (Icterohaemorrhagiae, Canicola, Grippotyphosa, and Pomona) vaccines, rather than 2-serovar vaccines; and AAHA Canine Vaccination Guidelines since 2011 do not recommend the use of 2-serovar products.

Leptospiral vaccines are generally considered serovar-specific, and cross-protection between serovars should not be assumed. This concept is being challenged in some research, however, and cross-protection may occur between selected serovars. Recent research suggests that MAT seropositivity for serovars Autumnalis, Grippotyphosa, Bratislava, and Pomona are strongly correlated. Thus, there appears to be some molecular mimicry between these serovars. At Purdue, we have not documented a case of leptospirosis attributable to serovar Bratislava or Autumnalis in a dog properly vaccinated with a 4-serovar product, again suggesting some cross-protection may occur between some serovars.

Which dogs should be vaccinated? Several published studies in the last 10-15 years have found that leptospirosis cases were more likely to be dogs from suburban, or recently urbanized, areas than from rural settings. Wildlife studies at other universities indicate that population densities of peri-urban wildlife may be 8-12 times greater than in their rural counterparts due to increased availability of food and lack of predators, thus increasing disease exposure risk. A review of leptospirosis cases from the VMDB (Veterinary Medical Database) from university teaching hospitals over the last 40 years documents a change in the signalment in diagnosed cases, with dogs less than 15 pounds proportionately more likely to be diagnosed with the disease than dogs in other weight groups. These small dogs in our experience have not been vaccinated against leptospirosis, leaving them susceptible to infection. The pertinent patient history question is not “Does your dog live in the country?” but rather “Does your dog have potential exposure to raccoons, skunks or other wildlife (or specifically their urine) in your neighborhood or backyard?”

Other recent studies in the US and in Canada have documented increasing disease in small breed dogs. In fact, one study showed Labrador retrievers at reduced risk. These findings may merely be a reflection of vaccination protocols, i.e. sporting breed dogs are being vaccinated but small breed (so called ‘backyard’) dogs are not. Tying this finding with previous studies suggests: 1) urban wildlife such as raccoons and skunks are known carriers of leptospirosis, 2) wildlife populations are often denser in suburban/urban than in rural areas, and 3) small dogs can be exposed to this disease in their backyard due to wildlife activity.

All leptospiral vaccines are similar in that they are bacterins. Recombinant leptospirosis vaccines do not exist. Bacterins can vary in the quantity of whole inactivated bacteria or cell wall antigens present, or in quantity of vaccine excipients (such as bovine serum albumin) remaining from vaccine production. This variation in exogenous protein/antigen most likely explains the occurrence – or lack of occurrence – of allergic reactions following leptospirosis vaccination and observed differences in the rate of these reactions among vaccines by different manufacturers. Nevertheless, current vaccines are much improved in safety compared to the biologicals produced more than a decade ago. New 2022 AAHA Canine Vaccination Guidelines, while leaving leptospirosis as a noncore vaccine, strongly recommends considering it for all dogs and to start the vaccination series at 12 weeks of age or later. Advisory groups appear to be moving toward designating leptospirosis vaccines as core.

Manufacturers typically recommend 2 initial vaccines, and so these can be administered as part of final (rather than all or initial) puppy vaccinations. Annual revaccination is recommended, and supported by epidemiological studies. Because some dogs have low or undetectable

leptospiral antibodies at 12 (or even 6) months post-vaccination, the duration of immunity from leptospiral bacterins has been considered by some to be less than 1 year – even though manufacturers’ recommendations are for annual revaccination intervals. Evidence of 12-15 months of disease protection following leptospiral vaccination has been reported in the last decade, and is becoming accepted as the duration of immunity (DOI) for these vaccines. Although infection can occur in a properly vaccinated dog, this is quite uncommon and may reflect a high but less than 100% vaccine efficacy in large populations.

Concern has occasionally been raised regarding data from vaccine trials indicating that vaccinated dogs may develop renal carriage if challenged/exposed to infection. If this is true, there should be documentation of transmission of infection from vaccinated dogs; but such evidence is lacking. Closer examination of experimental data however indicates that the challenge dose of leptospires in vaccine trials probably far exceeds the natural exposure dose. Also, documented renal carriage or leptospire shedding has been noted predominantly with serovar Canicola, the serovar for which the dog is a natural reservoir. Although a chronic-shedding state for dogs remains to be proven by culture, viable organism can be shed in acutely ill dogs - presenting a public health risk to owners, families, and veterinary staff.

Some concern has also been raised about concurrent administration of bacterins with modified live virus (MLV) vaccines. This concern is based on a single research study documenting lower post-vaccinal viral antibody titers after administration of a bacterin compared to no bacterin. The clinical significance of this finding is questionable. All vaccines marketed as multivalent vaccines with leptospiral bacterin as a component with viral vaccines, e.g. distemper or

parvovirus, have been tested in challenge studies to be efficacious for each component of the multivalent vaccine – as required by USDA. Clinical experience, i.e. lack of disease “breaks”, also supports the assumption of no decline in efficacy/protection with concurrent vaccinations.

Infections should be treated with a 2-week course of doxycycline, unless they cannot tolerate oral medications. In these cases, initially administer parenteral ampicillin or amoxicillin (IV preferred). Infected dogs are not considered to be of zoonotic risk after 48 hours of antibiotic administration. The soon-to-be-released 2023 Updated ACVIM Consensus Statement on Leptospirosis in Dogs will have more information about the use of dialysis in dogs with severe oliguria/anuria.

What about cats? Does leptospirosis affect cats, and cause clinical disease? Although cats can have exposure to leptospires via rodents or urine-contaminated water (and cats are well known to get kidney disease), published diagnoses of feline leptospirosis have been uncommon in veterinary medical literature until recent years. Cats can, and do, produce titers against leptospirosis; but seropositivity rates in cats are much lower than found in dogs. Some studies have also noted there was no significant difference in seropositivity for cats with kidney disease compared to cats without a history of kidney disease – again suggesting no significant disease impact in this species. Potential explanations include greater innate immune protection against initial infection and subsequent reduced viability of the organism in the feline renal/urinary system.

The testing of cats for leptospires by PCR has recently renewed professional interest in many countries in feline infection. Several studies have noted PCR-positive results in a small percentage of tests of cat urine. The risk of false-positive PCR results should always be considered however by other-than-*Leptospira* organisms or by non-viable *Leptospira*. A critical review of the literature does note that ascites was a physical examination finding on some of the reputed feline cases of leptospirosis. Whether this is a manifestation of a leptospiral-induced vasculitis remains to be determined. Nevertheless, clinical disease in cats appears to be highly uncommon. If diagnostic testing is believed warranted, the use of paired acute and convalescent sera to document a 4-fold rise in MAT titer is recommended. Most titers in cats, if they occur, are very low and would not invoke a positive in-house test result.

An excellent recent literature review on investigations into feline leptospirosis is:

Murillo A, Goris M, Ahmed A, Cuenca R, Pastor J. Leptospirosis in cats: Current literature review to guide diagnosis and management. *J Feline Med Surg*. 2020;22(3):216-228.

doi:10.1177/1098612X20903601

Other references available on request

The 2010 ACVIM Consensus Statement on Canine Leptospirosis: *J Vet Intern Med*.

2011;25(1):1-13. doi:10.1111/j.1939-1676.2010.0654.x is in final stages of revision, and the update will probably be published in JVIM online on/about January 2024.