PEER REVIEWED

CANINE LEPTOSPIROSIS
A Perspective on Recent Trends

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From prevalence to risk factors to diagnosis and therapy, this article explores the latest information on this zoonotic disease.

Leptospirosis has been described as a re-emerging disease in both dogs and humans.[1,2]

Whether or not a true increase in the incidence of canine leptospirosis (**Figure 1**) has occurred over the past 2 decades is unclear. Increased awareness and vigilance, partly spurred by educational campaigns, have likely increased the number of diagnosed cases. Still, several studies have suggested a temporal trend that is consistent with a re-emergence of leptospirosis.[3]

In either case, leptospirosis should be recognized as a significant infectious disease in dogs, with variable incidence that is dependent on unpredictable short- and long-term weather patterns and influenced by anthropogenic factors that may affect exposure of dogs to wildlife vectors.

SEROGROUP PREVALENCE

There has been much discussion about the changing face of serogroup prevalence in dogs—from Canicola and Icterohemorrhagiae (1950s to 1970s) to Grippotyphosa and Pomona (1990s to present day). The reality is that serogroups Grippotyphosa and Pomona were well-described in dogs in reports dating back to 1956.[4,5] Similarly, Birnbaum, et al, did not see any change in serogroup prevalence from 1980 through 1995, with serogroups Grippotyphosa and Pomona predominating.[6]

Serogroup prevalence more likely

Figure 1. *Scanning electron micrograph of* Leptospira *species; notice the corkscrew appearance of the bacterium.*

reflects geographic influences on the sampled population. It is important to emphasize that serogroup Icterohemorrhagiae appears to be the most common cause of leptospirosis in dogs and humans in certain cities, such as Baltimore, Detroit, New York City, and St. Louis, where the Norway rat remains the predominant vector. In most other parts of the United States, serogroup Grippotyphosa and, to a lesser extent, serogroup Pomona predominate.[7,8,9]

RISK FACTORS

Understanding risk factors that affect the incidence of leptospirosis in any region helps increase a veterinarian's index of suspicion with regard to canine patients that present with clinical signs and laboratory analysis consistent with leptospirosis.

A number of recent studies have used geospatial analysis of various hydrographic and land cover features to better define these risk factors. When interpreting the findings of these studies, awareness of the pitfalls associated with them is crucial; however, a few common themes have emerged:

- **Rural environments:** Although exposure to wildlife/livestock and walking in rural environments have been supported as risk factors in 2 studies, other studies have noted that dogs living in urban areas are at greater risk.[7,10-13]
- **Urban environments:** Urban wildlife that may contribute to this higher risk is commonly presumed to be rats and raccoons. In addition, recent reports have raised the concern that bats may be a significant source of transmission due to their abundance and proximity to domestic animals.[14]
- **Water proximity & exposure:** Most studies agree that proximity and exposure to water bodies and frequently flooded areas are risk factors for leptospirosis in dogs. Flooding, in particular, liberates leptospires from urine-contaminated soil, resulting in exposure to dogs and humans.
- **Weather:** Most every study has reported an increased incidence of canine leptospirosis in the fall months, although cases are reported for every month of the year.
- **Predispositions:** There have been conflicting findings on the age, gender, and breeds of dogs that are at increased risk, suggesting that all dogs are susceptible to leptospirosis. German shepherd dogs may be at increased risk; however, it is unclear whether this is a true breed-specific susceptibility.

CLINICAL SYNDROMES

Acute Kidney Injury

The most common syndrome associated with canine leptospirosis is acute kidney injury (**Figures 2 through 4**), which can manifest clinically as:

- Lethargy
- Anorexia
- Polyuria and polydipsia
- Vomiting.

In these dogs, azotemia can vary in severity and is usually dependent on the time between onset of clinical signs and presentation to the veterinarian for diagnosis and care.[15]

Leptospirosis was identified as the most common cause of acute kidney injury in a recent study, accounting for 31% (56/182) of all cases and 54% (98/182) when known causes (ethylene glycol, nonsteroidal anti-inflammatory drugs, and hemodynamic causes) were excluded.[16]

Liver Disease

The suspicion of leptospirosis is increased in dogs with acute kidney injury that have concurrent evidence of acute hepatocellular injury or cholestatic liver disease, which may manifest as increased serum alkaline phosphatase, with or without hyperbilirubinemia.

When hepatitis occurs without acute kidney injury, elevations in serum alanine transaminase and serum alkaline phosphatase occur with variable severity, along with hyperbilirubinemia.

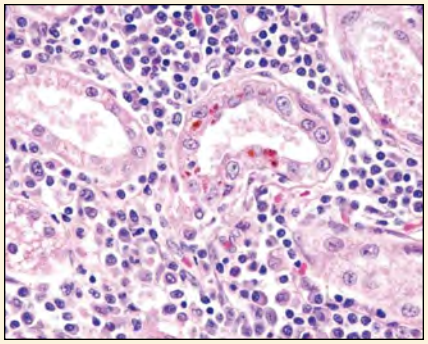

Figure 2. *Interstitial nephritis consisting predominantly of lymphocytic and plasmacytic inflammation, with low number of macrophages and neutrophils*

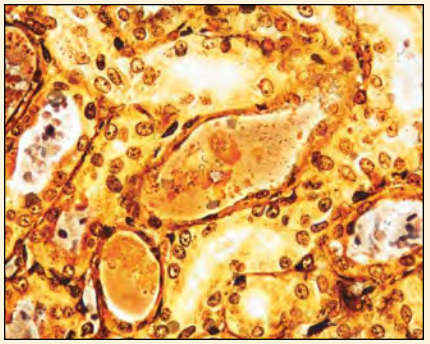

Figure 3. *Warthin-Starry silver stain demonstrating leptospiral organisms within the renal tubule*

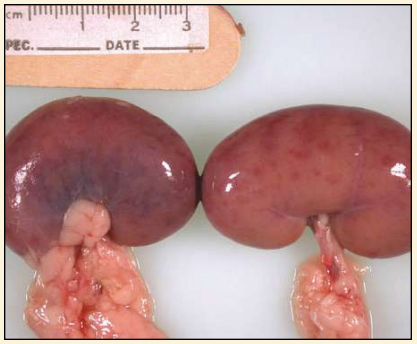

Figure 4. *Petechial and ecchymotic hemorrhages on the cortical surface of the kidneys*

Figure 5. *Diffuse small intestinal hemorrhage*

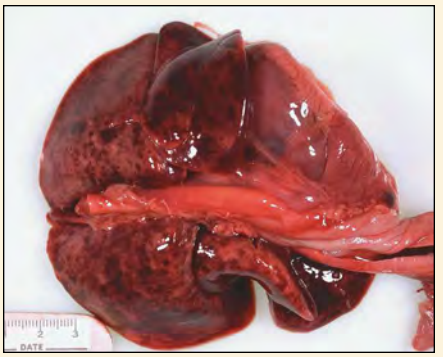

Figure 6. *Diffuse pulmonary hemorrhage*

Uveitis & Enteritis

Uveitis has been recognized as a concurrent finding in some dogs with either acute kidney injury or hepatitis, although it may be subtle and, therefore, undiagnosed in some cases.[17] Likewise, intussusceptions as a result of severe enteritis (**Figure 5**) have been reported as a rare concurrent condition in dogs with acute kidney injury.[18]

Polyuria & Polydipsia

Polyuria and polydipsia (PU/PD) in the absence of any routine laboratory abnormalities (other than hyposthenuria) is the second most common syndrome seen at my institution.[19] While these dogs appear outwardly healthy, they exhibit profound PU/PD. Many have a history of brief fever and lethargy that is self-limiting up to 2 weeks prior to onset of PU/PD; an event that can be easily overlooked.

Most causes of PU/PD are easily eliminated from the differential list based on:

- A normal CBC and serum biochemical profile
- The absence of active urine sediment (or negative urine culture).

Testing for leptospirosis should be performed prior to evaluation for central diabetes insipidus or psychogenic PD.

Pulmonary Hemorrhage

Recently, concern has been raised about the emergence of pulmonary hemorrhagic syndrome, which is seen in humans.[20,21] Reports of pulmonary hemorrhage in dogs with leptospirosis (**Figure 6**) can be found throughout the literature, but it is unclear whether it is truly emerging as a syndrome of significant incidence.

- **Concurrent syndromes:** Many, although not all, dogs with this syndrome have concurrent acute kidney injury.
- **Pathogenesis:** The alveolar hemorrhage is believed to be caused by vasculitis (which can affect other organs, see **Figure 7**), potentially complicated by thrombocytopenia; however, these are not consistently found, suggesting an alternate pathogenesis. It is not known whether the hemorrhage occurs secondary to local release of toxins, effect of circulating toxins, or an immune-mediated process.
- **Imaging:** A diffuse miliary, reticulonodular, or bronchointerstitial pattern is most commonly seen on radiographs.
- **Supportive therapy:** Some of these patients may require oxygen support during treatment for leptospirosis. No additional therapies are supported in the literature as being particularly effective in reducing mortality associated with this syndrome.

DIAGNOSTICS

Confirming a diagnosis of leptospirosis is limited to 2 noninvasive tests, based on high sensitivity and specificity, reasonable cost, and speed of turn-around:

- Microscopic agglutination test (MAT) (**Figure 8**)
- Polymerase chain reaction (PCR).

Microscopic Agglutination Test

The MAT has long been the standard for leptospirosis diagnosis and is available through most commercial, state, and veterinary college diagnostic laboratories.

- **Diagnostic titers:** Ideally, a 4-fold increase in the serum titer documented over a 2- to 4-week period is preferred to confirm a diagnosis, although

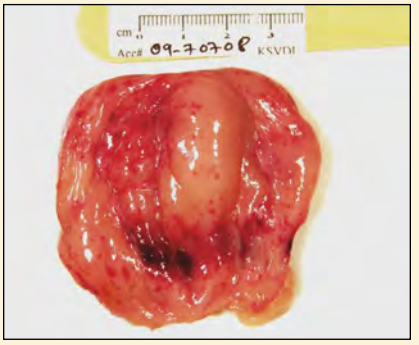

Figure 7. *Edema and hemorrhage of the urinary bladder*

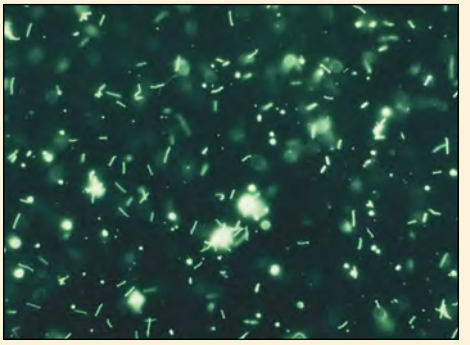

Figure 8. *Photomicrograph of leptospiral microscopic agglutination test with live antigen, using darkfield microscopy technique*

a single titer taken during the acute stages of disease, along with compatible clinical signs, is often accepted as diagnostic.

- **Single titer variations:** Defining an acceptable cutoff for a single serum titer can be difficult and may vary based on the serogroup evaluated, previous leptospiral vaccinations, and other infections, which may result in false positive results.
- **Reciprocal titer cutoffs:** While a reciprocal titer of 800 is often used in the literature, prior vaccination may produce a reciprocal titer of 6400, suggesting that a cutoff reciprocal titer should be set at 12,800.[22,23]

MAN VERSUS DOG: ZOONOTIC IMPLICATIONS

A recent study evaluated the seropositivity of dog owners and veterinary staff that were in contact with dogs with clinical leptospirosis. The results showed that none of the people seroconverted, suggesting that the risk of zoonotic transmission from dogs is low.[1]

Determining Source. However, there are a number of well-documented cases of humans contracting leptospirosis from dogs. In fact, the asymptomatic carrier may pose a more significant risk to humans as individuals may not take the same precautions (ie, wearing gloves, judicious hand washing) as when handling a dog showing clinical signs of leptospirosis. It should also be noted that humans and dogs may become infected from the same source, resulting in the incorrect assumption that the dog was the source of infection.

Reducing Risk. Zoonotic risk can be reduced by vaccination; good hygiene (hand washing after contact with healthy or ill dogs); and avoiding contact with urine, saliva, or feces from infected dogs. Certain conditions and occupations may predispose humans to leptospirosis, including rodent exposure, unsanitary living conditions, water-related recreation (boating, triathlons, kayaking), abbatoir or sewer maintenance, work with livestock, and certain farming practices (sugar cane, rice).

Assessing Disease Course. Although most infections in humans are symptomless, when clinical, the most common presentation is acute, febrile illness that mimics influenza, with fever, chills, headache, nausea, and myalgia. Illness may be followed by resolution, transient improvement with relapse, or progressive disease.

Those with progressive disease may develop recurrent fever, aseptic meningitis, jaundice, renal failure, or uveitis. A smaller percent of cases may develop fulminant disease, which may include hepatic and renal disease (Weil's syndrome), hemorrhagic pulmonary syndrome, or septic shock.

1. Barmettler R, Schweighauser A, Bigler S, et al. Assessment of exposure to *Leptospira* serovars in veterinary staff and dog owners in contact with infected dogs. *JAVMA* 2011; 238(2):183-188.

Results of the MAT have been used to suggest the epidemiologic prevalence of certain serogroups.

- However, recent studies have cast doubt on the reliability of the MAT to accurately predict the infecting serogroup in humans, with the MAT correctly identifying the infecting serogroup only 33% to 44% of the time.[24,25]
- Miller, et al, recently reported dismal results when looking at agreement of MAT results with 5 veterinary diagnostic laboratories (VDLs), although the true infecting serovar was not known.[22]
  - » The VDLs only agreed on titers in 31% of vaccinated, specific pathogen-free dogs and 27% of patients with clinical cases of leptospirosis.
  - » Equally disturbing, over the course of long-term follow-up with 6 dogs, the VDLs identified different serogroups in each dog.
  - » Although this did not affect diagnosis of leptospirosis in these dogs, the MAT did not provide reliable information regarding the infecting serogroup—information that may be important in evaluating vaccine options.

Polymerase Chain Reaction

PCR has been shown to have good sensitivity and specificity in the diagnosis of leptospirosis.[19,23]

- **Sample selection:** While a variety of body fluids (blood, urine, cerebral spinal fluid, aqueous humor) and tissues (kidney, liver) can be used, urine is most commonly used due to its ease of acquisition and high concentration of organisms in infected dogs, even those without acute kidney injury.[26,27]
- **Organism shedding:** The onset of clinical signs in dogs is such that, at the time of presentation, the leptospiral organisms are being shed in the urine of most dogs.
- **Serovar identification:** PCR cannot currently identify infecting serovars, but laboratories report the presence or absence of pathogenic leptospires. In the near future it appears that PCR will be able to identify serovars, vastly improving its utility by providing information with epidemiological significance.

THERAPY

There are 2 main therapeutic components for leptospirosis in dogs:

- Appropriate antimicrobial therapy
- Management of organ failure.

Antimicrobial Therapy

A number of antimicrobials have been demonstrated to be effective in killing leptospires, at least through *in vitro* studies. However, the most frequently recommended antibiotics for dogs with leptospirosis are ampicillin and doxycycline.

- **Ampicillin** (22 mg/kg IV Q 8 H) is recommended

as first-line therapy for dogs in acute renal failure. It is effective at resolving the leptospiremic phase (presence of leptospires in the blood), but not the leptospiruric phase (presence of leptospires in the urine). For that reason, dogs should be transitioned to doxycycline once they can tolerate oral antibiotics.

Editor's Note: Intravenous doxycycline can be substituted for ampicillin as initial therapy (10 mg/kg IV Q 24 H, diluted and administered as a slow infusion).—*Dr. Lesley King, Editor in Chief*

- **Doxycycline** (5 mg/kg PO Q 12 H) should be administered to the dogs mentioned above as well as those that are eating, such as dogs with nonazotemic PU/PD.
  - » I recommend a 3- to 4-week course of doxycycline.
  - » In dogs in which azotemia does not resolve completely after 2 weeks of doxycycline, I recommend performing a PCR assay to determine if the organism has been cleared.
  - » If PCR is positive, the dog should be treated with a fluoroquinolone.[28,29]

Management of Organ Failure

Supportive care for dogs with acute kidney injury is focused on adequate fluid therapy.

Most dogs with acute kidney injury have **polyuric** renal failure. Adequate fluid therapy can be ensured by establishing an acceptable weight range following rehydration; then weighing the dog every 4 to 6 hours to monitor for marked deviation from this target weight.

For patients that are **oliguric**, the placement of a urinary catheter and closed collection system may be necessary for accurate measurement of urine production. A central venous catheter may also be necessary to ensure that overhydration does not occur.

Additional management strategies, such as use of diuretics in oliguric dogs and guidelines for anti-emetics and gastroprotectants, can be found in reference textbooks.

Complications

- **Persistent vomiting** should be initially managed with maropitant or metoclopramide (however, not in the presence of intussusception).
- In patients with **abdominal pain and vomiting caused by renal pain**, which can be intense, the administration of an opioid, such as buprenorphine or fentanyl, is recommended.
- In the presence of **renal or hepatic failure**, gastric hyperacidity may also contribute to vomiting; an H2-receptor blocker (eg, famotidine) should be administered.

Referral to a center that can perform hemodialysis or peritoneal dialysis is recommended for dogs that:

- Remain oliguric or anuric for longer than 24 hours, presuming that they have been adequately hydrated

- Demonstrate fluid overload
- Fail to convert to PU with the administration of furosemide.

PREVENTION

The veterinarian has to evaluate a number of factors when deciding whether to offer leptospirosis vaccination to their clients:

- Is it necessary?
- Will it be effective?
- Is it safe?

Necessity is driven by the incidence of disease in a particular geographic area, but that information is often not readily available. Veterinarians need to be aware of the ubiquitous nature of leptospirosis, usually endemic in rodent and raccoon populations, and consider the risk factors in their locale.

All evidence supports that vaccination is effective in preventing clinical disease and renal shedding in dogs. Safety can be a concern, especially in small dogs if multiple vaccines are co-administered, although adverse reactions are uncommon. I recommend administering the leptospirosis vaccine as a stand-alone vaccine, at a time independent of other vaccines.

CONCLUSION

Leptospirosis is a significant zoonotic disease in most geographic areas.

- Veterinarians should make this a top differential diagnosis in cases of acute kidney injury when the cause is not immediately evident or known.
- Efforts to diagnose leptospirosis and sharing results of a positive diagnosis with other veterinarians in the area should (1) increase awareness of the disease and (2) help determine risk level of leptospirosis in specific geographic regions. ■

LEARNING ABOUT LEPTOSPIROSIS

- **ACVIM Consensus Statement:** onlinelibrary.wiley.com/doi/10.1111/j.1939-1676.2010.0654.x/full
- **AVMA Media Library:** avmamedia.org/display.asp?sid+397&NAME =Leptospirorsis
- **AVMA Client Brochure:** avma.org/2011/10/21/new-leptospirosis-brochure/
- **Centers for Disease Control & Prevention:** cdc.gov/leptospirosis or cdc.gov/leptospirosis/pets
- **Leptospirosis Information Center:** leptospirosis.org
- **The Merck Veterinary Manual:** merckvetmanual.com/mvm/index.jsp?cfile =htm/bc/51203.htm
- **World Health Organization:** who.int/leptospirosis/en

MAT = microscopic agglutination test; PCR = polymerase chain reaction; PD = polydipsia; PU = polyuria; VDL = veterinary diagnostic laboratory

FIGURE NOTES

- **Figures 2, 3, 5, and 6** are from a 2-year-old, spayed female golden retriever with oliguric renal failure from leptospirosis (urine PCR, positive; serum titer to Grippotyphosa, 1:12,800). This dog also had thrombocytosis (794,000 platelets/mcL; reference range, 200,000–500,000/mcL) on initial laboratory analysis 3 days before euthanasia.
- **Figures 4 and 7** are from a 3-month-old, intact female bichon frise with acute renal failure and cholestasis from leptospirosis (urine PCR, positive; acute serum titers, negative). Platelet count in this dog was within the reference range on presentation.

FIGURE CREDITS

- **Figure 1** reprinted with permission from Kenneth Latimer, PhD, Diplomate ACVP; from University of Georgia's Noah's Arkive collection of figures (**vet.uga.edu/vpp/noahsarkive/na_order.php**)
- **Figures 2 through 7** courtesy of Gordon Andrews, DVM, PhD, Diplomate ACVP, Department of Diagnostic Medicine and Pathobiology, College of Veterinary Medicine, Kansas State University

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