LEPTOSPIROSIS

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Leptospirosis, a thin, motile spirochete with a hook-shaped end, is a zoonotic disease that affects wildlife, companion animals, and livestock. There are over 200 serovars of Leptospira, with some being saprophytic while others are pathogenic. Numerous reservoir hosts exist for Leptospira including raccoons, voles, skunks, dogs, pigs, cattle and rats, resulting in growing exposure to humans and to the environment. In dogs, leptospirosis is caused by Leptospira interrogans (including serovars icterohaemorrhagiae, canicola, pomona, bratislava, and possibly autumnalis) and Leptospira kirschneri (including serovar grippotyphosa). Prior to vaccines (developed in the 1960s), the most common serovars infecting dogs including L. icterohaemorrhagiae and L. canicola. More recently, different serovars seem to be more associated with canine leptospirosis, including L. grippotyphosa, pomona, bratislava, and possibly autumnalis. Currently, veterinary vaccines provide coverage against L. icterohaemorrhagiae, L. canicola, L. grippotyphosa and L. pomona. With canine leptospirosis, infection with certain serovars are thought to be associated with certain types and severities of clinical disease, although this is not definitive. L. pomona appears to result in more severe renal disease and worse outcome (50% as compared to 78-81%) as compared to other serogroups.

GEOGRAPHIC DISTRIBUTION
The prevalence of leptospirosis is higher in warm, tropical locations with high rainfall. The top geographical locations where humans are diagnosed with leptospirosis include the Caribbean, Latin America, India, Southeast Asia, Oceania, and Eastern Europe. In North America, Hawaii is the state with the highest human cases. In the United States, high antibody prevalence (≥1,600) has been seen in dogs from the following regions: Hawaii, West coast states (e.g., northern California, Oregon, Washington), the upper Midwest (e.g., Minnesota, etc.), the Northeast, the mid-Atlantic coastal regions, and other regions (e.g., Texas, Colorado).

RISK FACTORS
While canine leptospirosis used to be considered more prominent in large breed, male, working dogs that free roam in rural environments, more recent studies have found that urban areas have a growing prevalence, with smaller dogs < 15 pounds being one of the fastest growing populations of canine leptospirosis. Of increased concern are studies showing that >20% of dogs may be chronic healthy carriers (based on studies in Michigan). Additional risk factors for leptospirosis include exposure to slow-moving or stagnant water, conditions where higher rainfall has occurred, late autumn, exposure to urbanized wild animals, or rodent exposure. One hypothesis is that global warming has contributed to the growing prevalence of leptospirosis due to the creation of warmer, wetter (e.g., flooding) weather conditions. Likewise, urban sprawl – the invasion of humans into the environment of wildlife - has increased the prevalence of canine leptospirosis.
While rare, leptospirosis has been reported in cats.\textsuperscript{10} Serologic evidence of exposure has been confirmed in cats to \textit{L. canicola}, \textit{L. grippotyphosa}, and \textit{L. pomona}.\textsuperscript{1} Exposure is thought to occur due to rodent exposure,\textsuperscript{1} and can result in clinical illness and histopathologic changes consistent with changes seen in dogs with leptospirosis.

**TRANSMISSION**
Pathogenic leptospires are shed from renal tubules of both domestic and wild animals,\textsuperscript{1} and can remain viable in the soil and environment for weeks to months.\textsuperscript{11} That said, leptospires are inactivated by UV radiation and freezing.\textsuperscript{1} Infection can also occur through intact mucous membranes or abraded skin with direct or indirect exposure to urine.\textsuperscript{1} Rarely, leptospirosis can be transmitted via bite wound, ingestions of infected tissue (e.g., eating raw meat), or by venereal or placental transfer.\textsuperscript{1}

**CLINICAL SIGNS**
Canine leptospirosis classically presents with both acute kidney injury (AKI) and hepatic injury. Clinical signs include:

- Generalized malaise/listlessness
- Inappetance to anorexia
- Vomiting
- Halitosis (e.g., uremia)
- Hypersalivation
- Diarrhea
- Melena
- Icterus
- Febrile
- Dehydration
- PU/PD\textsuperscript{*}
- Abdominal pain (e.g., secondary to AKI)
- Uveitis
- Conjunctivitis
- Oliguria/anuria
- Weight loss

\textsuperscript{*}Note, the polyuria and polydipsia seen with canine leptospirosis may be seen irrespective if the patient is azotemic.\textsuperscript{1} This may be due to several causes: impaired renal concentrating ability secondary to a decreased glomerular filtration rate or decreased vasopressin responsiveness of the inner medullary collecting ducts (e.g., acquired nephrogenic diabetes insipidus).\textsuperscript{1}

Less common signs include hematuria, vasculitis (e.g., peripheral edema, pleural effusion, ascites, etc.), cardiac abnormalities, abortion (e.g., predominantly reported in cattle), and pulmonary signs.\textsuperscript{1} Pulmonary lesions may be secondary to leptospiral pulmonary hemorrhage syndrome (LPHS) or vasculitis.\textsuperscript{1} Clinical signs include tachypnea, dyspnea, acute respiratory distress syndrome (ARDS), and pulmonary hemorrhage. With leptospirosis, a secondary coagulopathy may also be seen due to hepatic failure (e.g., decreased production of activated


Vitamin K factors II, VII, IX, and X), disseminated intravascular coagulation (DIC), or vascular damage (e.g., presumed to be secondary to the spirochetes). Clinical signs of coagulopathy include:

- Petechial hemorrhage
- Hemoptysis
- Melena
- Epistaxis
- Hematochezia
- Hematemesis

**DIAGNOSTIC TESTING**

The diagnosis of leptospirosis is based on clinical suspicion, clinical signs, and clinicopathologic results consistent with leptospirosis. Clinicopathologic findings consistent with leptospirosis include the presence of: neutrophilia, a left shift, lymphopenia, a mild to moderate non-regenerative anemia, hemoconcentration (seen with dehydration), hemolysis (seen with cattle), thrombocytopenia (seen in up to 58% of dogs), azotemia (seen in > 80-90% of dogs), increased liver enzymes (including increases in ALT, AST, ALP, and total bilirubin; these changes are almost always seen with concurrent azotemia with leptospirosis), electrolyte abnormalities (e.g., hypokalemia, hyponatremia, hypochloridemia, hyperphosphatemia), and increased creatinine kinase. Additional findings consistent with leptospirosis include isosthenuria, bilirubinuria, hematuria, glucosuria, proteinuria, and evidence of coagulopathy (e.g., increased fibrinogen, FDP, FSPs). Prolonged PT or PTT may be seen in 6-50% of dogs with leptospirosis. Other advanced diagnostics may include radiology (to look for evidence of pulmonary lesions secondary to leptospirosis, which may appear as a nodular interstitial or alveolar pattern) and abdominal ultrasound (to rule out other underlying disease processes such as neoplasia, etc.). Ultrasound findings may reveal non-descript findings including renomegaly, pylectasia, perirenal fluid accumulation, a medullary band of increased echogenicity, increased cortical echogenicity, and rare other findings (e.g., splenomegaly, mild abdominal lymphadenopathy, etc.).

The most “definitive” diagnosis of leptospirosis is typically based on serology by the microscopic agglutination test (MAT), which tests for antibodies to leptospires. The MAT tests for the highest serum dilution causing agglutination of 50% of the leptospires. MAT testing typically includes *L. canicola*, *L. icterohaemorrhagiae*, *L. pomona*, *L. grippotyphosa*, *L. hardjo*, and *L. bratislava*. Unfortunately, there are several limitations of the MAT, including the hazardous need to maintain live cultures of pathogenic serovars, difficulty in standardizing the test, expense, cross-contamination of serovar cultures, and false negatives (e.g., due to acute disease) or false positives (due to previous vaccination, exposure, etc.). Another limitation of the MAT is that some cross-reactivity may occur between different serogroups. Keep in mind that one of the key limitations of MAT is that during the first week of acute disease, dogs may test negative. For this reason, convalescent titers are generally recommended 2-4 weeks later (at the same laboratory) to look for the presence of seroconversion. Typically, a 4-fold increase in titer is suggestive of infection; however, recent vaccination or antimicrobial therapy may affect the results (e.g., antimicrobial therapy may blunt the expected response). Interpreting MAT results must be done with care, as a result. Titers post-exposure can persist for at least one year, but are thought to declined by 4 months secondary to vaccination.
There are other diagnostic tests that can be used to screen for leptospirosis including dark field microscopy, silver staining of biopsy specimens (e.g., renal), immunohistochemistry, PCR, in situ hybridization, culture, leptospirosis PCR & antibody ELISA in-clinic test. A newer Zoetis WITNESS in-house rapid IgM antibody test is also recently available.\textsuperscript{13, 14} Note that each has their limitations. Dark field microscopy is technically difficult and has low specificity; this has fallen out of favor and is rarely used now. Silver staining of renal biopsy tissue can be performed, but lacks sensitivity and can result in false negatives. Fluorescent antibody testing and PCR can be performed on urine or tissue. Note that culture, PCR, and even antibody ELISA tests can all be affected by recent microbial therapy. For this reason, pre-treatment blood work should always be utilized for submission in the patient suspected to have leptospirosis.

**TREATMENT**

Treatment of the leptospirosis patient is aimed towards fluid therapy, antibiotic therapy, gastrointestinal support, supportive care, and monitoring.

**Fluid therapy**

In the leptospirosis patient, aggressive intravenous (IV) fluid therapy is indicated as many patients are often massively polyuric, dehydrated, and azotemic. In general, a balanced, maintenance, isotonic crystalloid (e.g., LRS, Norm-R) can be used at 2.5-4.5X maintenance, and monitoring of ins and outs may be necessary to guide treatment (based on the severity of polyuria seen in patients with leptospirosis). The patient should be assessed carefully to ensure that volume overload does not occur, particularly in patients with cardiopulmonary disease. Fluid therapy should be continued until azotemia and clinical signs resolve (typically 2-4 days); IV fluids should then be slowly tapered to ensure that polyuria has resolved and the patient can maintain hydration.

**Goals of fluid therapy**

Serial physical examination is imperative to adequately evaluate a patient’s hydration status—checking for return of skin turgor, appropriate weight gain, and moisture of mucous membranes. However, physical examination findings are subjective, and <5% dehydration is subjective and difficult to assess on physical examination. The concurrent use of evaluation of PCV/TS, blood glucose, blood urea nitrogen (BUN or AZO), weight, urine output (UOP), urine specific gravity (USG), and thirst can be used in conjunction with physical examination findings to better assess hydration status.

**Packed Cell Volume/Total Solids, Blood Glucose, and Blood, Urea, Nitrogen (BUN/AZO)**

Patients on IV fluids should have daily blood work (including PCV/TS, blood glucose, electrolytes, renal or biochemistry panel) assessed while hospitalized. Because patients often experience hemoconcentration when they are dehydrated (e.g., PCV/TS 55%/7.8 g/dL; 78 g/L), the goal of fluid therapy is to ensure that these numbers improve with appropriate therapy (consistent with hemodilution). Ideally, the PCV/TS in a normal, systemically healthy patient on IV fluids at sea level should be 35%/5.0 g/dL (50 g/L). In fact, oxygen delivery is maximal at such a “hemodilute” PCV/TS, as there is less viscosity of red blood cells and “sludginess.” Note that some patients with leptospirosis may have a mild to moderate non-regenerative anemia; the goal should still be to hemodilute the patient, and total protein/solids should be used as a more appropriate guide in this situation. We can still evaluate the PCV/TS in abnormal, metabolically
inappropriate patients. Classically, a 10% to 12% dehydrated, cachectic, geriatric cat with chronic renal failure may present to you with a PCV/TS of 28%/11 g/dL (110 g/L). Once that patient is adequately hydrated, the PCV/TS may decrease to 20%/7 g/dL (70 g/L), unmasking the anemia from lack of erythropoietin.

**Urine Specific Gravity (USG)**

In normal healthy patients, USG can be evaluated in patients on IV fluids to help assess hydration status. Ideally, USG should be measured before fluid administration to allow for evaluation of renal function. Dehydrated patients with concentrated urine demonstrate adequate renal function (cat > 1.040, dog > 1.025) - in other words, the kidneys are working and trying to absorb as much water from the urine as possible. Once started on IV fluids, normal, systemically healthy patients should have isosthenuric urine. Patients on IV fluids for > 6 to 12 hours should have adequate dilution of USG, and the ultimate goal of fluid therapy and adequate hydration should be USG of 1.015 to 1.018 on IV fluids. Patients on IV fluids with USG > 1.020 are still likely dehydrated and should be treated more aggressively with IV fluids if other parameters of dehydration persist (e.g., hemoconcentration). Hydration can be determined by assessing the color, volume, and USG of urine. A patient that is still dehydrated while hospitalized on IV fluids may have decreased UOP and dark-yellow urine (provided, for example, that no pigmentation, myoglobinuria, or bilirubinuria are present). This is a result of antidiuretic hormone release and renin-angiotensin stimulation, resulting in maximum absorption of free water and sodium. Unfortunately, in the leptospirosis patient, PU/PD may occur due to acquired nephrogenic diabetes insipidus, so utilizing USG as a guideline for hydration status will be difficult.

**Urine Output (UOP)**

UOP should be monitored carefully, particularly in azotemic patients with leptospirosis. Fluid therapy should be directed toward achieving a hydrated state and matching ins and outs, based on the patient’s UOP. Note that normal UOP is 1–2 ml/kg/hour, but many of these leptospirosis patients present with severe polyuria. Again, one can assess the hydration status of the patient by evaluating the volume and USG of urine. Excessive urination with dilute, clear urine may indicate copious or excessive IV fluid therapy, whereas hypersenthuria may suggest ongoing dehydration, and aggressive fluid resuscitation may be further warranted. If UOP is decreased (particularly in azotemic patients), fluid therapy and vasopressor support (to increase renal blood flow) should be initiated to prevent anuria (< 0.5 ml/kg/hour) or oliguria (< 1 ml/kg/hour). If UOP is decreasing and renal function is normal (based on creatinine, BUN, and pre–fluid therapy USG), the patient should be reassessed for hydration status, and fluid therapy adjusted as indicated.

- Normal UOP: 1–2 ml/kg/hour
- Oliguria: 0.5–1 ml/kg/hour
- Anuria: < 0.5 ml/kg/hour

Note that underlying diseases such as leptospirosis; postobstructive diuresis (posturethral obstruction); diabetes mellitus (with secondary osmotic diuresis due to glucosuria); diabetes insipidus; hyperthyroidism (increased glomerular filtration rate due to increased metabolic rate); and chronic renal failure (inability to adequately concentrate and absorb water) may result in
dramatic water losses through the kidneys, and these patients may need a higher rate of fluids to compensate for ongoing losses. Likewise, these disease processes prevent us from differentiating renal versus prerenal disease on the basis of USG alone, as these patients have isosthenuria due to metabolic disease. Regardless, appropriate fluid therapy and urine monitoring (e.g., “measuring ins and outs”) may be necessary, particularly in azotemic, oliguric renal failure.

**Antibiotic therapy**
In the patient suspected of having leptospirosis, prompt, appropriate antibiotic therapy should be initiated (ideally after pre-treatment blood work has been submitted). Goals of antibiotic therapy is to eliminate leptospiremia and to eliminate leptospires from the renal tubular cells and renal carrier state). Appropriate antibiotics include penicillins (e.g., including ampicillin, amoxicillin, amoxicillin/clavulanic acid, penicillin, etc.) and doxycycline. In humans, the use of ceftriaxone and cefotaxime are also efficacious. The use of fluoroquinolones is controversial, as efficacy in a hamster model failed to clear leptospires from the kidneys and blood. Based on the ACVIM Consensus Statement, the antibiotic of choice is doxycycline (5 mg/kg PO or IV q. 12 hours for 2 weeks). Leptospires can shed in urine for months if appropriate antibiotic use is not implemented.

**Gastrointestinal support**
Azotemic patients should be treated with phosphate binders (e.g., aluminum hydroxide) if hyperphosphatemic, along with gastrointestinal protectants (e.g., omeprazole, pantoprazole, famotidine, sucralfate, etc.) for presumptive uremic gastritis. Anti-emetics (e.g., maropitant, ondansetron, dolasetron) should be implemented for patient comfort and to treat nausea.

Anti-emetics:
- Maropitant: 1 mg/kg SQ q. 24 hours
- Ondansetron: 0.1-0.2 mg/kg IV q. 8-12 hours
- Dolasetron: 0.5-1 mg/kg SQ, IV q. 24 hours
- Metoclopramide: 0.1-0.5 mg/kg SC, IV q. 8 hours or 1-2 mg/kg/day as CRI IV

**Gastric pH altering medication:**
H₂ blockers:
- Famotidine: 0.5-1 mg/kg IV, SQ q. 12-24 (least p-450)
- Ranitidine: 0.5-2 mg/kg, IV, PO, SQ q. 8-12 (moderate p-450)
- Cimetidine: 5-10 mg/kg IV, PO, SQ q. 6-8 (most p-450)

Proton-pump inhibitors:
- Omeprazole: 0.5-1 mg/kg PO q. 24 hours
- Pantoprazole: 1 mg/kg IV q. 24 hours

**Anti-ulcer:**
Sucralfate 100-1 g PO q. 8 hours

**ZOONOTIC RISKS**
In animals developing acute leptospirosis, caution must be taken to prevent zoonotic spread. The use of appropriate hygiene (including protective eye wear, gowns, gloves, etc.) should be used
when handling the patient and bodily fluids while hospitalized. Pet owners should also be cautioned about the zoonotic risk. A 10% bleach solution, iodine-based disinfectant, accelerated hydrogen peroxide, and quaternary ammonium solutions can all be used against leptospires.¹ Likewise, other pets in the house should be assessed for clinical signs, and if healthy, vaccinated to mount an immune response.

PROGNOSIS

The prognosis for leptospirosis is fair to good, provided aggressive treatment can be initiated. The survival is reported to be approximately 80% in dogs, both with dogs treated conservatively (e.g., IV fluids) and those treated more aggressively with hemodialysis.¹ In those dogs developing pulmonary complications, the prognosis is poorer, with reported mortality rates (from Europe) of 36-42%.¹ Pet owners should be cautioned about the risks for chronic renal insufficiency as a secondary consequence of chronic renal inflammation.

PREVENTION

As shedding of organisms can persist (e.g., leptospuria) for weeks to months, prevention is imperative. Despite the good prognosis for leptospirosis, aggressive preventative care is warranted in dogs. This will help minimize zoonotic risk to pet owners and veterinary professionals; help minimize the chronic carrier state in dogs (which can result in further spread); prevent costly hospitalization; and minimize the risk of chronic injury (chronic renal failure). A leptospirosis prevention package should be initiated with the following:

- Environmental changes: This should be initiated to include rodent control; appropriate fencing; and landscaping changes to remove stagnant/standing water.
- Annual vaccination: The decision to vaccinate should be based on an endemic area, exposure of the dog, and risk factors (e.g., access to streams/stagnant water or urbanized wildlife). Ideally, vaccination with a 4-way leptospirosis strain should be utilized. Vaccination is important to help prevent/aid in the prevention of shedding to reduce infection of other animals and possible human exposure.

REFERENCES

2. Winzelberg SE. Leptospirosis treatment and prevention with data on an ongoing leptospirosis prevalence study at the Animal Medical Center in New York City. Atlantic Coast Veterinary Conference Proceedings, 2013.

NOTE: When in doubt, all drug dosages should be confirmed and cross-referenced with a reference guide such as Plumb’s Veterinary Drug Handbook.