LEPTOSPIROSIS: CLINICAL FEATURES AND PRESENT DAY THREAT

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INTRODUCTION

Leptospirosis is a life-threatening disease to dogs, but rarely reported to occur in cats. The clinical importance of this disease is significant because it is also zoonotic. The diagnosis of leptospirosis in dogs in the United States and Canada increased substantially between 1983 and 1998.1 In the United States, leptospirosis in dogs has traditionally been associated with Leptospira interrogans serovars canicola and icterohaemorragiae. Use of vaccines containing these serovars has reduced the incidence of disease attributable to them. 2,3 During the past 10 years, however, there has been an increase in the number of dogs with leptospirosis from which clinicians have isolated or detected serologic evidence to support the involvement of L. kirschneri serovar grippotyphosa, L interrogans serovar bratislava, and L. interrogans serovar pamona.1,2,4 Leptospirosis is distributed world wide and effects many species, including human beings. Serovars known to be pathogenic to dogs (and their reservoir hosts) include: australis (rodents), autumnalis* (mouse), balum (mouse), bataviae (dog, rat, mouse), bratislava (pig, horse), canicola* (dog), icterohaemorragiae* (rat), grippotyphosa* (raccoon, skunk, opossum, small rodents), hardjo* (cow), and pomona* (pig, cow, skunk, opossum). Serovars that occur commonly in human cases are shown with an asterisk (*). Although leptospirosis was once thought to occur primarily in dogs in rural areas, this is no longer true due to ubiquitous nature of reservoir species.

PATHOGENESIS

Leptospirosis may cause vasculitis, myositis, hepatitis, acute renal failure, and uveitis. Dogs are exposed from contaminated water, urine, food, bedding, and bite wounds. The organisms penetrate the mucous membranes, wounds, or abrasions, and multiply. If the immune system cannot eliminate or contain the organisms, vasculitis and thrombocytopenia occur within the first 6 days. After this period, the organisms replicate in the renal tubular cells causing acute renal failure. Hepatitis, vasculitis, DIC, menigitis, uveitis, abortion, and fertility may also occur. After 14 days, the organisms are shed in the urine. Animals that do not die of leptospirosis eventually clear the organisms from the kidneys or become chronic carriers.

CLINICAL SIGNS AND LABORATORY FINDINGS

Leptospirosis may present as peracute, acute, subacute, or chronic disease. Clinical signs depend on the serovar, the individual’s immune response, and how quickly treatment is instituted. Large breed (>15 kg) male, outdoor, middle-aged dogs are affected most commonly.5 Peracute leptospiral infections can cause death and very few clinical signs. Acute infections are often associated with pyrexia, shivering, and muscle tenderness; vomiting, dehydration, and shock quickly follow. Coagulopathy and vasculitis may be observed with hematemesis, hematochezia, melena, epistaxis, and petechiation. Terminally ill dogs become depressed and hypothermic; hepatic and renal failure is not typically present. Subacute infections are thought to be the most commonly recognized form of leptospirosis. This is manifested with pyrexia, anorexia, vomiting, dehydration, and polydipsia. Myalgia and paraspinal hyperesthesia may result from muscular, meningeal, or renal inflammation. Mucous membranes appear injected, and petechiation and ecchymoses are present. Conjunctivitis, rhinitis, and tonsillitis are usually accompanied by cough and dyspnea. Acute renal failure develops and is associated with polyuria/polydipsia, which may progress to oliguria or anuria. Most dogs (83-100%) present in renal failure. 2,3,8 The degree of azotemia vary with severity of disease and degree of dehydration. Hyperphosphatemia, metabolic acidosis, and hyperkalemia occur, and the hyperkalemia is often associated with oliguria or anuria. On urinalysis, glucosuria, proteinuria, and active sediment (pyuria, hematuria, and cylindruria) may be present. Abdominal imaging studies may reveal renomegaly. Ultrasonography of the kidneys may show a bright demarcation between the cortex and medulla (medullary rim sign) and possibly perinephric fluid.2,7 Gastrointestinal signs tend to more severe and persistent in dogs with leptospirosis compared with other causes of acute renal failure. Melena and hematochezia are often noted. Respiratory signs may occur in a small number of dogs with leptospirosis (3-20%).6,8 Thoracic radiography reveals a patchy alveolar or nodular pattern or generalized interstitial disease predominating in the caudodorsal lung fields. Pulmonary hemorrhage, edema, acute respiratory distress syndrome, and interstitial pneumonitis have been observed to occur.7,8 Leukocytosis with or without a left shift and thrombocytopenia are often present. Liver failure is usually less severe than renal failure, although was a prominent part of historical leptospirosis. Increased activities of alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase, and hyperbilirubinemia occur typically with liver involvement. Peak increase is usually 6 to 8 days after onset of disease. Many dogs with leptospirosis have chronic or subclinical disease. Dogs with fever of unknown origin, unexplained renal and/or hepatic disease, polyuria/polydipsia, or uveitis should be tested for leptospirosis. Additionally, healthy dogs in kennels, multi-dog households, neighborhoods, or other areas where infection has been documented should be screened and monitored for signs of leptospirosis.

DIAGNOSIS

Darkfield Microscopy – Darkfield microscopy can detect live leptospires in a wet mount of fresh urine. A minimum of 10^5 organisms/mL must be present. Unfortunately, there are many false positives and false negatives with this technique.

MAT – The MAT is the standard serological test used for diagnosing leptospirosis. Serial dilutions of sera are mixed with leptospiral organisms, and the highest dilution that agglutinates 50% of the organisms is recorded. Most laboratories start with a dilution of 1:100, and further two-fold dilutions are performed to the end-point. This test is somewhat serovar specific. The highest titer is considered the infecting serovar, with lower positive titers considered to be cross-reactivity. Commonly tested serovars include icterohaemorragiae, canicola, pomona, grippotyphosa, and hardjo. A single titer ≥ 1:800 is sufficient for a diagnosis of leptospirosis if the dog has clinical signs consistent with
leptospirosis and was not vaccinated for leptospirosis in the previous 3 months. Negative or low titers (≤ 1:32)
0) often persist for a few moths following vaccination; however, post-vaccinal titers can be high (≥ 1:3200). Serology may be negative early in the course of disease; therefore, convalescent titers 2-4 weeks later are often required for confirmation. A four-fold increase in antibody titer is confirmatory.

ELISA, Fluorescent Antibody, and PCR – Several ELISA tests are available for rapid diagnosis in human beings and dogs. These are not usually serovar-specific, and a positive test must be confirmed by MAT. Fluorescent antibody techniques have been developed to test for leptospires in body fluids (eg blood, urine) or tissue imprints; however, they do not distinguish between serovars. PCR testing is available for leptospirosis DNA (University of Illinois, Kansas State University), however, is has not been thoroughly evaluated.

TREATMENT
Specific – Antimicrobial therapy should be instituted in all dogs suspected of having leptospirosis. It is directed at initially clearing the leptospiremic phase and subsequently at clearing the leptospiruric (carrier) phase. High doses of penicillin (Penicillin G procaine – 40,000-80,000 U/kg IM or SQ q24hr or divided q12hr; continue for 2 weeks or until azotemia resolves; dose may require adjustment with renal failure), ampicillin (20 mg/kg IV q6-8hr), or amoxicillin (20 mg/kg PO q8hr; difficult to use while patient is uremic) are used during the leptospiremic phase. There are no randomized prospective studies concerning the best antimicrobial agent. Doxycycline (5 mg/kg PO q12-24hr for 2 weeks) may also be effective in clearing leptospiremia and is the antimicrobial of choice for clearing the leptospiruric phase.

Supportive – Supportive treatment is important in managing a dog with leptospirosis. Treatment is directed at correcting the excesses and deficiencies associated with acute renal failure and principles of treating acute renal failure include: minimizing further renal injury, replacing volume deficits as quickly as possible without inducing volume overload, correcting hyperkalemia and other electrolyte disturbance, correcting acid-base disturbances, initiating diuresis if needed, managing systemic signs of uremia, and monitoring and adjusting treatment.

Fluid therapy is paramount in managing dogs with acute renal failure due to leptospirosis. Many animals are oliguric or anuric at start of treatment because dehydration induces a physiological oliguria; therefore, determination of actual urine output cannot be made until the animal is rehydrated. Fluid therapy consists of 3 components: amount necessary for rehydration, maintenance fluid requirements, and amount necessary to offset ongoing losses (eg vomiting, diarrhea). Crystalloids are used for rehydration and should be administered intravenously over 4-12 hours depending on cardiovascular status. Once rehydrated, decrease fluid rate to maintenance plus ongoing losses (if present) plus 5-10% and monitor urine output. If non-oliguric (urine output > 1 ml per kg of body weight per hour), then balance fluid intake with measured or estimated urine output. Because transmission of leptospirosis is through urine, caution should be used in handling urine from an infected dog. Placement of a urinary catheter may aid in monitoring urine output. Alternatively, weighing the dog q4-8hr can give indirect assessment of volume status.

If oliguria is present (urine output < 1 ml per kg of body weight per hour) then try to convert to non-oliguria. This can only be diagnosed and attempted after the animal is rehydrated. Mannitol is an osmotic diuretic that causes volume expansion by pulling fluid into the vascular space. It improves renal blood flow, GFR, and tubular flow throughout the nephron, and decreases endothelial and tubular epithelial cell swelling. It is administered at 0.5-1 g/kg IV over 20-30 minutes. Do not use if the patient is overhydrated, and do not administer more than 2 doses. Furosemide is a loop diuretic that increases sodium excretion at the level of the ascending loop of Henle resulting in increased tubular flow rate. It also increases renal blood flow, but does not affect GFR. Furosemide is administered in incrementally increasing doses starting at 2-3 mg/kg IV up to 35 mg/kg. It is synergistic with dopamine. Dopamine is a selective vasodilator at low dose constant rate infusion. It causes afferent and some efferent vasodilation and increases sodium and water excretion by the kidneys. Dopamine is administered at a CRI of 1-5 mcg/kg/min. If necessary, dialysis (hemodialysis or peritoneal dialysis) may be attempted to manage the oliguria and anuria until the patient recovers.

Hyperkalemia occurs with oliguria and anuria and may cause bradycardia, dropped P waves, and eventual ventricular escape beats with possible ventricular tachycardia. If hyperkalemia persists after fluid replacement therapy or if clinical signs are present, then it should be treated. Hyperkalemia can be decreased by promoting a shift of potassium from the vascular compartment into cells using glucose (10% glucose – 4-10 ml/kg IV), glucose and insulin (0.5 U/kg regular insulin + 4 ml of 50% dextrose/U of insulin IV), or sodium bicarbonate. If ECG abnormalities are present, calcium gluconate (10% calcium gluconate – 0.5 ml/kg IV slowly) can be administered to counteract the effect at the sino-atrial node. Many animals with acute renal failure have a metabolic acidosis. Volume replacement and diuresis often corrects this. Occasionally, sodium bicarbonate administration may be required; however, it is not needed unless blood pH is < 7.2.

Uremic gastroenteritis occurs commonly with leptospirosis-induced acute renal failure. It may result in dehydration due to vomiting, overall malaise of the patient, and blood loss if active ulcer disease. Histamine-2 receptor blockers (ranitidine – 1-2 mg/kg q12hr; or famotidine – 0.5 mg/kg q 12-24hr) are of benefit in decreasing gastric hyperacidity and counteracting effects of hypergastrinemia occurring with renal failure. Mucosal protectants may also be indicated and sucralfate is used to bind to exposed submucosa and to treat active ulcer disease. Nausea and vomiting is treated with anti-emetics such as metoclopramide (0.2-0.4 mg/kg SQ or IM q8hr or CRI of 1-2 mg/kg/d) or chlorpromazine (0.2-0.3 mg/kg SQ or IM q12hr).

Nutritional support using the parenteral should be considered and may aid in overall recovery of the patient from acute renal failure due to leptospirosis. Some patients may require blood product administration. If anemia is severe due to blood loss, packed red blood cells or whole blood may be administered. If DIC is present, then plasma or platelet-rich plasma with heparin therapy may be required. Hypoalbuminemia and edema may be present due to vasculitis and plasma or other colloids may be required to increase plasma oncotic pressure.
OUTCOME

Survival rates for dogs with leptospirosis range from 78-88%; however, survival rate may be different in different parts of the country. Although many dogs recover completely, some will be left with residual chronic renal failure (33-40%). Patients that fail medical management and require hemodialysis have a survival rate of 80%.

PREVENTION

Vaccines containing multiple serovars are available and confer immunity only to the serovars contained in the vaccine. Early bivalent bacterins were produced from chemically inactivated whole cultures, which made them relatively allergenic. A newer subunit vaccine was released in 2000. Proteins from the outer envelope of the leptospiral organism are extracted and purified, discarding the cellular debris. This method of manufacture creates a vaccine that induces a protective antibody response while decreasing risk of an allergic reaction. This vaccine contains serovars icterohemorrhagiae, canicola, pomona, and grippotyphosa. Dogs in endemic areas or that travel to endemic areas especially high risk dogs (large breed dogs that are allowed to roam) should be vaccinated. Initial series of vaccination should include a minimum of three injections 3 to 4 weeks apart. Booster vaccinations are recommended annually and sometimes biannually in animals in highly endemic areas.

HUMAN HEALTH IMPLICATIONS

The most likely source of infection for human beings is contact with infected urine from a dog with leptospirosis, especially by owners who care for the pet at home and for hospital personnel who care for the pet during aggressive treatment. Animals suspected with leptospirosis should be handled appropriately. Latex gloves should be worn when handling urine or urine-contaminated items (eg urinary catheters). Hands should be washed thoroughly after contact with infected dogs. Face masks and goggles should be worn by persons hosing contaminated kennels or cages. Areas contaminated with infected urine (eg floors, cages) should be disinfected with an iodophor-based compound (eg povidone-iodine). Iodophors are iodine solutions complexed with surfactants or polymers, which help increase contact of iodine with the surface to be disinfected while limiting concentrations of free iodine. The disinfectant should remain in contact with the area for 15 minutes before removing.

Suggested procedures for handling leptospirosis suspects in the hospital include:

1. place the dog in a run or bottom cage and do not remove them;
2. when possible, use disposable bedding until the suspect has received at least 3 days of antimicrobial therapy;
3. gloves and gowns should be worn when handling the patient and face masks and goggles should be worn when hosing down the run or cage;
4. Wash hands thoroughly after handling patient;
5. all material in contact with the patient’s urine (eg urinary catheters, bedding, gloves, etc) should be placed in a biohazard container for disposal;
6. place the dog on a cart if it needs to be transported to another area of the hospital (eg radiology) and use disposable bedding under the animal in case of urination;
7. thoroughly disinfect any area where the animal urinates outside of the run or cage; and
8. disinfect the run or cage with an iodophor disinfectant and do not use for 24 hours after the patient leaves.

REFERENCES