ETIOLOGY

Leptospirosis is a disease of humans and animals caused by infection with the motile spirochetal bacterium of the genus, *Leptospira*. Leptospirosis as a zoonotic disease worldwide cannot be overstated, because it causes human disease and deaths in much of the world, but mostly in areas of Asia and South America. The bacteria are highly motile, thin, flexible, and filamentous, made up of fine spirals with hook-shaped ends. Motility is gained by writhing and flexing movements while rotating along the long axis. The bacterium is an obligate aerobic spirochete that share features of both gram-negative and gram-positive bacteria.

Many classification methods have been used to divide up the pathogenic leptospires into more workable groups. An antigenic classification scheme used in the past divided them into distinct serogroups based on surface antigens, each containing one or more serovar. Newer classification schemes are based on genetic methodologies. Today, most of the commonly diagnosed canine pathogenic serovars are still classified (as before) as belonging to the *Leptospira interrogans* species, although the common canine serovar grippotyphosa is typically classified as belonging to the *L kirschneri* species.

Approximately 250 different serovars have been identified in the *Leptospira* complex. Many of the isolates are of unknown clinical importance in any species. Six to eight serovars are thought pathogenic in the dog. Each serovar has a primary or definitive host that maintains the organism and contributes to its dissemination in the environment. Although all mammals may be susceptible to infection, clinical signs are expected to be most severe with non-host-adapted serovars, whereas the definitive host is typically infected at a young age and is thought to most commonly exhibit minimal clinical disease.

Canine leptospirosis was first described in 1899. Before 1960, *L interrogans* serovars icterohaemorrhagiae and canicola were believed responsible for most clinical cases of canine leptospirosis. The disease then, mainly described as acute or subacute hepatic and renal failure, was often thought characterized by acute hemorrhagic diathesis,
icterus, or uremia. Because these serovars were considered the most common in dogs, they are also the ones found in the long-existing bivalent vaccines. After these vaccines came into widespread use, the incidence of classic leptospirosis in dogs, from these two serovars, seems to have decreased, although a cause and effect between the widespread use of the vaccine and the reduction of infection with these serovars has not been proved. In the past 20 years, several reports of increased incidence of the disease have been published with only a few cases of those classic serovars in North America in dogs (Table 1). The most common serovars today in the United States in reports are thought to be *L. kirschneri* serovar grippotyphosa, *L. interrogans* serovar pomona, and *L. interrogans* serovar bratislava. The recent increase in the diagnosis of the disease seems real, not just an effect of increased testing. Beginning in 2000, new vaccines have appeared on the market that include *Leptospira* serovars grippotyphosa and pomona. It is likely too soon to assess a potential serovar shift, if there is one, after the use of the newer vaccines. In recent years, increasing incidence of dogs testing serologically positive to *L. kirschneri* serovar autumnalis has also been documented as many commercial laboratories have added this serovar to their testing panel. Little is known about this serovar in the dog in terms of experimental infection, and it may emerge as an important cause of renal and nonrenal leptospirosis in the future, but it also seems a common serologic result even in vaccinated research dogs and in other dogs that have not been exposed to this serovar. Recent reviews assessing suspected serovar incidence in confirmed cases of leptospirosis in different regions of North America (see Table 1). Results of many reviews need to be examined carefully, however, because they are usually based on serosurveys typically using the microscopic agglutination test (MAT), which is likely a poor predictor of the true infecting serovar. Other serovars have been documented in different parts of the world. Serogroup Australis has also been incriminated in an outbreak in Canada and has been documented as the cause of chronic hepatitis in dogs in France and leptospirosis in Italy. In Germany, the predominant serovars seem to be grippotyphosa, saxkoebing, icterohaemorrhagiea, canicola, and bratislava; a recent survey in Italy identified serovars bratislava and grippotyphosa.

**EPIDEMIOLOGY**

There are two types of mammalian hosts when it comes to *Leptospira* infections. Each serovar is adapted to one or more mammals as a primary, also called the definitive or

<table>
<thead>
<tr>
<th>First Author (Region)</th>
<th>Journal</th>
<th>Year</th>
<th>No. of Cases</th>
<th>Predominant Serovars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein (New York)</td>
<td>JVIM</td>
<td>2006</td>
<td>55</td>
<td>Grippotyphosa, Pomona</td>
</tr>
<tr>
<td>Ward (Indiana)</td>
<td>JAVMA</td>
<td>2004</td>
<td>90</td>
<td>Grippotyphosa</td>
</tr>
<tr>
<td>Prescott (Ontario)</td>
<td>Can Vet J</td>
<td>2002</td>
<td>31</td>
<td>Autumnalis, Bratislava</td>
</tr>
<tr>
<td>Adin (California)</td>
<td>JAVMA</td>
<td>2000</td>
<td>36</td>
<td>Pomona, Bratislava</td>
</tr>
<tr>
<td>Ribotta (Quebec)</td>
<td>Can Vet J</td>
<td>2000</td>
<td>19</td>
<td>Prippotyphosa, Pomona</td>
</tr>
</tbody>
</table>

reservoir, host. Adapted resevoir hosts are thought to harbor persistent infection, often without severe signs of disease and can shed organisms in their urine for months to years after infection. The bacteria are maintained in the renal tubules of reservoir hosts and excreted in the urine. The other type of mammalian host is the incidental host that becomes infected with a specific serovar that is not adapted to living chronically in this species of mammal. Incidental hosts tend to develop clinical disease and either clears the organisms or die; rarely do they develop a chronic carrier state.

The dog serves as the reservoir host only for the pathogenic *L. interrogans* serovar canicola. The reservoir hosts for the other serovars include common rodents, skunks, raccoons, farm animals, and deer, which can carry and excrete the bacteria in their urine for extended periods. The incidence of the canine chronic carrier state for *Leptospira* organisms is unknown. If this state exists, it is likely to specifically exist for dogs infected with *L. interrogans* serovar canicola. It is less likely, and even less clear, whether or not such a carrier state exists in dogs infected with other serovars that have not adapted for persistence in the dog and are more commonly seen at least in the ill canine population today.

Leptospires can be transmitted directly between hosts in close contact through urine, venereal routes, placental transfer, bites, or ingestion of infected tissues as the organism penetrates mucosa or broken skin. Shedding by infected animals occurs, usually via urine. The exact duration of shedding and potential spread to other dogs or humans is uncertain and may depend on the serovar. Indirect transmission, which probably happens more frequently, occurs through exposure of susceptible animals or humans to a contaminated environment, where the organisms persist after exposure from the urine of an infected host. Water contact is the most common means of spread, and habitats with stagnant or slow-moving warm water favor organism survival. Even in rapid moving water, however, it seems that the organism survives in high concentration in the shallow areas or adheres to rocks and other debris. The invasion of the *Leptospira* organisms into the host is via skin wounds or through intact mucous membranes. The organism survives only transiently in undiluted acidic urine (pH 5.0 to 5.5) as neutral to basic pH is favorable for its survival. Dilute or non-concentrated urine provides a suitable habitat. Freezing markedly decreases survival of the organism outside the host, likely contributing to a seasonal pattern of infection in colder climates. Ambient temperatures between 0°C and 25°C favor survival of the organism. Therefore, rainfall, temperature, and pH requirements may explain the apparent increased incidence of canine leptospirosis in late summer and early fall, in the southern, semitropical belt of the United States, and in similar climatic regions worldwide. Seasonality in many parts of the country is associated with rainfall. Reports exist of disease outbreaks occurring during or immediately after periods of flooding. In a large recent human outbreak in triathletes in Illinois, people became infected after swimming in a lake a short time after strong rains and flooding occurred, which likely washed bacteria into the shallow areas of the lake creating puddles on the shore that had been contaminated from raccoon urine.

After penetration in a susceptible host, leptospires begin to multiply as early as 1 day after entering the blood vascular space. This initiates a leptospiremic phase, which lasts a few days involving rapid replication of the bacteria and endothelial damage. After this phase, invasion of a variety of end organs, including the kidneys, liver, spleen, central nervous system (CNS), eyes, and genital tract can occur. Leptospires damage organs by replicating and inducing cytokine production and inflammatory cell invasion. The initial replication mainly damages the endothelial cells and only later the kidneys and liver. The extent of damage to internal organs varies seems to depend on the virulence of the organism, including serovar and strain, the inoculum, and host susceptibility.
Recovery from infection seems to depend on the production of specific antibodies. As serum antibodies increase, the organism is thought to be cleared. Based on experimental studies, renal colonization occurs in most infected dogs that do not have adequate protection from prior exposure or vaccination. Data are lacking regarding the incidence of chronic renal colonization in naturally infected dogs.

PATHOGENESIS

The sequence of events after infection seems amazingly variable and likely depends on

- Virulence, serovar, and perhaps even strain in addition to numbers of bacteria infecting the host. The author and colleagues have recently shown that suspected *L. interrogans* serovar pomona infections induced significantly more severe kidney disease and had a worse outcome than infection suspected to be from other serovars in a study of naturally occurring leptospirosis in dogs in New York State.\(^7\)
- Immune response. Previous exposure (naturally occurring or vaccinal) to the same serovar is likely to provide some degree of immunity although the duration of immunity after natural infection and the degree of cross protection between serovars are unknown in dogs. Immunity, however, is not predicted by MAT titers and seems to last at least 1 year after vaccination. A recent study comparing different commercially available vaccines showed only a mild serologic response to a series of two vaccinations but good immunity when challenged 1 year after the second vaccine.\(^25\)

After the leptospiremic phase, the following organs are typically targeted by the bacteria:

- The kidneys: renal colonization occurs in most experimentally infected dogs.\(^25\) Organisms persist and multiply in the tubular aspect of the renal tubular epithelial cells causing cytokine release, inflammatory cell recruitment, and acute nephritis. It is unclear how often this leads to the development of a chronic carrier state with urinary shedding. The likelihood of this occurring is thought significantly higher when the infecting serovar is canicola, because it is adapted to the dog as the primary host. Interstitial nephritis may be a chronic manifestation of acute disease in dogs.
- The liver: centrilobular necrosis and subcellular damage, bile canaliculi, and duct occlusion are thought to occur and may cause icterus. This was thought a common occurrence in serovar icterohaemorrhagiae and may not be as common today.\(^7\)
- Endothelium: tissue edema and disseminated intravascular coagulation may occur within the first few days of infection as a result an acute endothelial injury.\(^26\)
- Additional body systems may also be damaged during the acute phase of infection. A benign meningitis is produced when leptospires invade the CNS. The incidence in dogs of CNS involvement is unknown; however, it is well documented in humans. Uveitis may occur in naturally occurring and experimentally induced canine leptospirosis in addition to abortion and infertility resulting from transplacental transmission of leptospires.\(^26\) Pulmonary manifestations can be severe in canine leptospirosis. Clinically, these dogs experience labored respiration and coughing. Lung changes in dogs with leptospirosis are associated with pulmonary hemorrhage, most likely due to endothelial damage and vasculitis.\(^24\) Secondary immune-mediated disease (polyarthritis, hemolytic anemia, and so forth) has been suspected to occur but the true incidence of canine cases is unknown.\(^26\)
DIAGNOSIS

Achieving as definitive a diagnosis as possible should be of special importance to veterinary practitioners because of the zoonotic potential of the disease and the possibility of the dog serving as a reservoir for other dogs and humans. Unfortunately, achieving a definitive diagnosis is often difficult with the tools in use today. The first difficulty faced is that the clinical signs associated with this disease are often vague and are typically nonspecific. The clinicopathologic data are often more of a function of the end-organ damage and nonspecific as well. Subtle abnormalities and combinations of abnormal clinicopathologic data are often the key for a high index of suspicion necessary in these cases. Specific leptospirosis testing in practice today is typically still limited to serology although PCR testing may become a more common modality in the future, especially for acute cases. The MAT serologic test commonly used today lacks both sensitivity (negative results early in the disease process) and specificity (reacts positively with vaccinal antibodies) when a single test is performed. Thus, a high index of suspicion is required and veterinarians most often have to submit repeated samples to obtain a definitive diagnosis.

SIGNALMENT AND HISTORY

Identifying dogs more likely to become infected with *Leptospira* organisms is important to narrow down the need for specific and sometimes expensive and repetitive testing. A profile of the kind of dog more likely to be infected is also beneficial when deciding which dogs should be vaccinated against the disease. There are likely large geographic differences in these considerations and so the region and season should be taken into account, although large amounts of epidemiologic data by region are lacking for most areas. Roaming dogs and dogs exposed to standing water possibly contaminated by wildlife urine are more likely to be exposed. Some studies suggest male dogs are more likely to develop the disease possibly for that reason. Anecdotally, however, it seems that even small dogs in some urban environments contract the disease, forcing veterinary practitioners to be aware of possible regional differences, to maintain a wide index of suspicion, and to think broadly when dogs present with appropriate clinical signs and when making vaccine decisions.

CLINICAL SIGNS

Clinical signs of dogs with leptospirosis can vary from subclinical or minimal clinical disease or mild fever to severe kidney, liver, and pulmonary disease. The literature is biased by the testing that was performed in each study, meaning that if only test azotemic dogs are tested, then all dogs diagnosed will be azotemic. It seems, however, that subtle to severe signs of kidney and liver damage as well as coagulation defects predominate. It is unknown what percentage of naïve naturally infected dogs show obvious clinical signs, because subclinical disease is common in experimental infections. Peracute leptospiral infections have been produced experimentally and were characterized by massive leptospiremia, causing shock and often death. It is unknown how common this disease course is in naturally occurring cases. In a recent study of naturally occurring cases in New York State, the most common clinical signs included lethargy, vomiting, anorexia, and polydipsia. Abdominal pain, polyuria, and polydipsia were often striking in their magnitude. Overt icterus and fever on initial presentation were uncommon clinical signs and should not be relied on to determine which dogs should be tested for the disease.
CLINICOPATHOLOGIC DATA

Unfortunately there are few or no single clinicopathologic changes on a chemistry panel, complete blood count (CBC), or urine analysis that are pathognomonic for leptospirosis. Practitioners must take multiple, often subtle, abnormalities into account to try and build a case for the diagnosis of this disease in dogs. The most common abnormalities found in the chemistry panel of confirmed cases include azotemia, increased serum liver enzyme activity, electrolyte disturbances, and mild increases in serum bilirubin concentrations. Coagulation parameters may be altered in severely affected animals. The CBC abnormalities often include a mild to moderate leukocytosis and thrombocytopenia. Thus, a combination of these CBC abnormalities and azotemia or increased liver enzymes should be suggestive of leptospirosis. Signs of acute tubular injury, such as mild proteinuria and glucosuria, are often found on the urine analysis. 7,26

IMAGING

As in many types of infectious disease, imaging modalities of radiographs and ultrasound are helpful in ruling out additional causes of the clinical disease but are less helpful in confirming a diagnosis of leptospirosis. Characteristic changes have been described in the lungs on thoracic radiographs29,30 and in the kidneys on abdominal ultrasound31 in dogs with leptospirosis. Both of these studies were retrospective uncontrolled case series and it is unclear how often or how specific these findings are in dogs with this disease.

Thus, the decision to submit specific tests to attempt to confirm the diagnosis of leptospirosis is made based on the clinical picture that combines data from signalment, history, physical examination, and a broad minimal database. Fig. 1 represents a possible approach for diagnosing canine leptospirosis.

SPECIFIC TESTING

The most commonly used test today in veterinary practice in North America is the MAT.26 This test is performed by mixing serial dilutions of the canine sera with cultured Leptospira organisms of different serovars representing different serogroups. The titer against a specific serogroup is defined as the highest dilution of the sera that caused 50% or more agglutination of the organisms representing that serogroup. There are many inherent problems with the performance of this test. One is the possibility of subclinical infections and the persistence of antibodies, such that a positive test does not confirm disease. Perhaps more importantly, specifically for the diagnosis of leptospirosis, the MAT test does not differentiate between antibodies produced as a result of true exposure to the organism and antibodies produced after vaccination. An additional serious limitation to the diagnosis of leptospirosis with a single MAT titer is that in many cases this titer is negative at the time of initial presentation, falsely ruling out the disease if a single early titer is relied on. Negative initial antibody tests can be explained by the 7- to 9-day period required before MAT antibodies are detected. MAT titers become positive after approximately 1 week, peak at 3 to 4 weeks, and remain positive for months after both natural infection and vaccination.26 It has been assumed that a high MAT titer (>800) to a nonvaccinal serovar and a negative or low (<400) titers against vaccinal serovars, accompanied by clinical signs of leptospirosis, is typically considered highly suggestive of active infection.26 Although, in two studies where naïve puppies were given two different quadrivalent leptospiral vaccines, the MAT titers were often high or even the highest to the nonvaccinal serovar...
autumnalis\textsuperscript{30} (Midence and colleagues, ACVIM 2010\textsuperscript{12}). Therefore, a single reliable titer may only be when it is greater than 1:3200 for a vaccinal serovar and greater than 1:1600 for a nonvaccinal serovar.\textsuperscript{26} Another potential use of MAT titers is deciphering the likely infecting serogroup based on the serovar that gives the highest titer. This task is made difficult because of the large degree of cross-reactivity among serogroups so that the highest titers to a specific serogroup may not definitely identify the causative serovar. In a human study where urine cultures and MAT results were compared, the MAT accurately predicted serovar in only 46% of the cases.\textsuperscript{32} Another cofounding factor in the interpretation of the MAT test is the large degree of interlaboratory variation.\textsuperscript{26} Fortunately for veterinary practitioners, however, knowing the infecting serovar is not crucial information necessary for an appropriate diagnosis or treatment. It seems that all common serovars today in the dog population cause a clinically similar disease that is treated in an identical fashion regardless of the serovar.\textsuperscript{7,17} These data are important, however, from an epidemiologic and vaccine development standpoint.

Given these limitations of a single MAT titer, perhaps the most reliable way to use this test is to routinely perform a convalescent titer. A 4-fold change in a MAT convalescent titer when compared with baseline titers is consistent with active infection. Because antibody test results are often negative in the first week of illness, especially in young dogs (<6 months of age), a second serum sample should be obtained within 1 to 2 weeks. Therefore, to confirm current infection versus previous infection or vaccination, a change in titer should be demonstrated. Antimicrobial therapy early in the

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Fig. 1. Suggested flowchart for the current diagnosis of canine leptospirosis using the MAT. (*) Recommended serovars for testing in North America include grippotyphosa, pomona, bratislava, canicola, icterohemorrhagiae, and autumnalis. (From Goldstein RE. Leptospirosis in veterinary internal medicine expert consult. In: Ettinger SJ, Feldman EC, editors. Textbook of veterinary internal medicine expert consult. 7th edition. Saunders; 2010: p. 866 (Fig. 198–1); with permission.)
course of the disease may decrease the magnitude of the titer rise; therefore, the second sample should be obtained at 1 to 2 weeks after the first and not the typical 3-week convalescent window.

Direct isolation or identification of organisms is often the ideal mode of diagnosis in infectious disease. Direct culture of the organism from blood or urine is the gold standard. Unfortunately this is almost never performed in clinical veterinary medicine. The organism itself is hard to culture, requiring immediate placement in a special medium before any antibiotic therapy. Thus cultures cannot be performed on previously shipped urine at a referral laboratory. Cultures are also expensive and expose laboratory workers to possible exposure to the organism. Despite this, cultures should be encouraged in veterinary medicine because the data derived from culture confirmed cases are superior to those derived from serologically confirmed cases.

Direct visualization of the Leptospira organisms is possible in some cases. Darkfield microscopy has been used in the past in veterinary medicine for the diagnosis of leptospirosis in large and small animals. Unfortunately, this method lacks sensitivity and specificity and is not recommended today. Identification of the organism in paraffin-embedded tissue can sometimes be accomplished using Giemsa or modified Steiner (silver) stain, immunofluorescence, or immunohistochemistry. Because leptospirosis cases are rarely biopsied antemortum, these techniques on tissue are usually only made post mortem. Their use in body fluids, however, such as urine, when large amounts or organisms are present is possible as well. Polymerase chain reaction (PCR) is becoming a more common modality in the diagnosis of infectious diseases. Real-time PCR is the most sensitive and is currently commercially available in the United States. A combination of testing, both blood and urine, before antibiotic therapy is ideal because blood samples tend to be positive early in infection and then later the urine becomes positive. In two studies comparing PCR, culture, and antibody testing in healthy and diseased animals, PCR was significantly more sensitive than the other methods in identifying shedders and diagnosing the disease. Because of all the limitations of culturing, PCR may become the best approach for direct detection of the organism in the future, especially when testing for subclinical infection or chronic shedding. Recent advances in PCR techniques have allowed not only diagnosis of leptospirosis but also perhaps identification of specific Leptospira serovars. The use of real-time PCR is possible even in recently vaccinated dogs. In a recent study, two real-time PCR were not influenced by vaccinal DNA in these dogs. More data are required regarding the sensitivity and specificity of PCR in large numbers of naturally occurring cases before its true value is known. The current recommendation is to submit blood and urine before antibiotic therapy. Fig. 1 shows a possible diagnostic algorithm combining PCR and serologic diagnostics.

TREATMENT

Treatment of leptospirosis involves supportive care, treating the renal or hepatic manifestations of the disease, and the use of antimicrobials. Antimicrobial therapy should be started as soon as the disease is suspected and samples have been drawn (if PCR is submitted). This is essential to eliminate bacteremia and the potential for live organisms in the urine that pose a zoonotic risk to humans. This should be started before confirmation of the diagnosis. A study in humans revealed that if antibiotics were delayed by 7 days after presentation, there was no longer an advantage to their administration. The eventual goal of therapy is also to clear the organisms from tissue in addition to the blood and urine. The first goal of terminating bacteremia and sterilizing the urine can be achieved with doxycycline or a penicillin derivative. Doxycycline
seems the drug of choice for the clearing of the organism from tissue. Therefore, when the disease is suspected, if oral drugs can be administered, then doxycycline (5 mg/kg every 12 hours) or amoxicillin (22 mg/kg every 12 hours) can be used at that time. Ampicillin (22 mg/kg intravenously every 8 hours) or amoxicillin, if available for intravenous use (22 mg/kg every 12 hours), is preferred for dogs that cannot be given oral drugs initially. Shedding should be terminated within 24 hours of initiating antibiotics, greatly reducing the risk to humans and other dogs. Doxycycline (5 mg/kg orally every 12 hours for 3 weeks) is the drug of choice for clearing the organism from tissue or eliminating the carrier state. Doxycycline treatment should start as soon as oral therapy is possible if not used intravenously. Therefore, in a suspected case of leptospirosis, the common protocols include doxycycline alone for all animals that can tolerate oral therapy or a penicillin derivative that is switched to doxycycline after the diagnosis has been confirmed and the dog can tolerate oral medications.

Aggressive fluid therapy concurrent to the use of antibiotics is crucial to prevent and treat acute kidney damage. The extent of renal damage after treatment may play a key role in determining the long-term prognosis for affected dogs. Hemodialysis has been beneficial in dogs that develop anuria or oliguria or are refractive to fluid therapy. Some dogs have an apparent clinical recovery after treatment, whereas others develop persistent azotemia with an overall survival rate approaching 80% in most studies.

PREVENTION

Prevention ideally should start by limiting contact of pet dogs with wild animal reservoirs of the disease as well as sources of contaminated water. This is, of course, easier said than done, given the close contact of pets to wild animals, including rodents, even in urban areas. Thus vaccination is crucial to prevent the disease in at-risk dogs. All available vaccines are culture based and contained whole units or subunits of inactivated bacterins of serovars icterohaemorrhagiae and canicola. It is assumed, however, that these vaccines are not cross-protective against the serovars responsible for most of the current infections in dogs. To date, two bacterin-based vaccines that also contain serovars grippotyphosa and pomona as quadrivalent products are now on the market in the United States. These vaccines are recommended used annually after a two-injection initial series in a puppy or previously unvaccinated dog. Good protection has been shown to persist for 1 year despite very low MAT antibody titers at the time of challenge for other bacterin type of vaccines containing serovars icterohaemorrhagiae and canicola; recently, similar results have been presented regarding serovar grippotyphosa. Anecdotally, leptospiral vaccines have been thought to have a high incidence of allergenic reactions, especially in certain breeds, such as dachshunds and pugs. In a recent study, however, a quadrivalent leptospiral vaccine was not more reactive than other bacterin-based vaccines, including the vaccine used to prevent Lyme disease.

SUMMARY

Leptospirosis is a common zoonotic disease with a worldwide distribution. Dogs become infected by exposure to contaminated urine from shedding wild animals. The bacteria penetrate mucus membranes cause endothelial damage in organs, such as the liver and kidneys. The clinical signs and clinicopathologic data are nonspecific and a high index of suspicion is needed by practitioners. Testing today is highly based on serology (MAT) and perhaps PCR. Treatment of leptospirosis involves supportive care and antibiotics, and prevention includes environmental steps and annual vaccination of dogs at risk.
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