Leptospirosis

Weil's syndrome,
Swamp fever, Mud fever,
Autumn fever (Akiyami),
Swineherd's disease,
Rice-field fever,
Cane-cutter's fever,
Hemorrhagic jaundice,
Stuttgart disease,
Canicola fever,
Redwater of calves

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Etiology

Leptospirosis is caused by various species of *Leptospira*, a spirochete in the family Leptospiraceae, order Spirochaetales. The classification of this organism is complex. Before 1989, all of the pathogenic isolates belonged to the species *Leptospira interrogans*, which contained more than 200 serovars in 23 serogroups. More recently, the genus *Leptospira* has been reclassified into 16 or more species. Pathogenic serovars are now found in the species *Leptospira interrogans*, *L. noguchii*, *L. santarosai*, *L. meyeri*, *L. borgpetersenii*, *L. kirschneri*, *L. weilii*, *L. inadai*, *L. fainei* and *L. alexanderi.* The new classification system can be confusing because both pathogenic and non-pathogenic serovars and serogroups occur in the same species and a single serovar or serogroup can occur within multiple species. In clinical laboratories, the older serogroup/serovar classification is often still used.

Geographic Distribution

Leptospira species are found worldwide; however, the the predominant serovars vary by geograhic region. The most common serovars in the United States are *L. canicola*, *grippotyphosa*, *hardjo*, *icterohaemorrhagiae* and *pomona*.

Transmission

Leptospirosis can be transmitted either directly between hosts or indirectly in the environment. *Leptospira* spp. can be ingested in contaminated food or water, spread in aerosolized urine or water, or transmitted by direct contact with the skin. The organisms usually enter the body through mucous membranes or abraded skin. They may also be able to penetrate intact skin that has been immersed for a long time in water. *Leptospira* spp. are excreted in the urine, and can be found in aborted or stillborn fetuses, as well as in normal fetuses or vaginal discharges after calving. They can be isolated from the male reproductive organs. Human cases have also been transmitted during sexual intercourse, by breast feeding, from rodent bites, and after laboratory accidents.

Leptospira spp. do not multiply outside the host. In the environment, they require high humidity for survival and are killed by dehydration or temperatures greater than 50°C. They can remain viable for a few to many weeks or months in contaminated soil and for several weeks in cattle slurry. They can remain viable in water for several months under laboratory conditions, but do not survive as well in river water under natural conditions.

Disinfection

Leptospira species can be inactivated by 1% sodium hypochlorite, 70% ethanol, glutaraldehyde, formaldehyde, detergents and acid. This organism is sensitive to moist heat (121° C for a minimum of 15 min) and is also killed by pasteurization.

Infections in Humans

Incubation Period

The incubation period in humans is usually 7 to 12 days, with a range of 2 to 29 days.

Clinical Signs

Human infections vary from asymptomatic to severe. Many cases are mild or asymptomatic, and go unrecognized. Some serovars tend to be associated more often with some syndromes (e.g., severe disease is often associated with serovar *icterohaemorrhagiae*). However, any serovar can cause any syndrome.

In humans, leptospirosis is usually a biphasic illness. The first phase, called the acute or septicemic phase, usually begins abruptly and lasts approximately a week. This phase is characterized by nonspecific signs including fever, chills, headache and conjunctival suffusion. Myalgia, which typically affects the back, thighs or calves, is often severe. Occasionally, a transient skin rash occurs. Other symptoms may include weakness, photophobia, lymphadenopathy, abdominal pain, nausea, vomiting, a sore throat, cough,

chest pain and hemoptysis. Mental confusion, neck stiffness and other signs of aseptic meningitis have been reported in this phase. Jaundice can be seen in more severe infections. These symptoms last for approximately 4 to 9 days, then are typically followed by a 1 to 3 day period during which the temperature drops and the symptoms abate or disappear.

The second phase of leptospirosis, called the immune phase, is characterized by the development of anti-*Leptospira* antibodies, and the excretion of the organisms in the urine. This phase can last up to 30 days or more, but does not develop in all patients. During the immune phase, the patient becomes ill again. Nonspecific symptoms seen in the first stage, such as fever and myalgia, recur but may be less severe than in the first stage of disease. Two forms of disease, icteric and anicteric, are seen.

Most infections are of the anicteric form. The most important symptoms in this form are associated with aseptic meningitis. A severe headache, stiff neck and other meningeal symptoms occur in approximately half of all patients, and usually last a few days. Occasionally, these signs may be present for up to two weeks. Less common symptoms include cranial nerve palsies, encephalitis, confusion and changes in consciousness. Deaths are rare in the typical anicteric form; however, a syndrome of fatal pulmonary hemorrhage, without jaundice, has recently been reported.

The icteric form is more severe. It occurs in 5-10% of all patients, is often rapidly progressive, and may be associated with multiorgan failure. The most commonly involved organ systems are the liver, kidneys and central nervous system (CNS). In the icteric form, there may be no period of improvement between the septicemic and immune phases. Jaundice can be severe and may give the skin an orange tone, but it is not usually associated with severe hepatic necrosis. Acute renal failure occurs in 16-40% of cases. Some patients also have pulmonary symptoms, with clinical signs ranging from cough, dyspnea, chest pain, and mild to severe hemoptysis, to adult respiratory distress syndrome. Cardiac involvement can result in congestive heart failure, myocarditis and pericarditis. Hemorrhages may also be seen; epistaxis, petechiae, purpura and ecchymoses are the most common signs, but severe gastrointestinal bleeding, adrenal or subarachnoid hemorrhage, and pulmonary hemorrhages can occur. Rare complications include stroke, rhabdomyolysis, thrombotic thrombocytopenic purpura, acute acalculous cholecystitis, erythema nodosum, aortic stenosis, Kawasaki syndrome, reactive arthritis, epididymitis, nerve palsy, male hypogonadism, Guillain-Barre´ syndrome and cerebral arteritis. Deaths can occur from kidney failure, cardiac involvement. pulmonary hemorrhage or other serious organ dysfunction. Convalescence from the icteric form may take 1-2 months. Although jaundice can persist for weeks, liver function returns to normal after recovery, and hepatic disease is rarely the cause of death. Most patients also recover kidney function.

Anterior uveitis occurs up to a year after recovery in 2-10% of cases. Most of these patients recover full vision. Iridocyclitis and chorioretinitis can also be complications, and may persist for years. Abortions, fetal death, and rare congenital infections in newborns have been reported. Abortions can occur at any time, including the convalescent period.

Communicability

Direct person-to-person transmission is rare but possible. *Leptospira* organisms are found in the urine during the second (immune) phase of the disease. Most people excrete these bacteria for 60 days or less, but shedding for months or years has been documented. Other routes of transmission are also possible: one infant was infected during breast feeding, and a case of transmission during sexual intercourse was reported.

Diagnostic Tests

Leptospirosis can be diagnosed by culture, detection of antigens or nucleic acids, or serology. Serum chemistry values and analysis of the CSF may support the diagnosis.

In humans, *Leptospira* can be isolated from the blood, cerebrospinal fluid or urine. Culture can be difficult and may require up to 13 to 26 weeks. Identification to the species, serogroup and serovar level is done by reference laboratories, using genetic and immunologic techniques. *Leptospira* spp. can also be identified in clinical samples by immunofluorescnce and immunhistochemical staining, as well as DNA probes and polymerase chain reaction (PCR) techniques. Darkfield microscopy can be used but is not specific.

Most human cases of leptospirosis are diagnosed by serology. The most commonly used serologic tests are the microscopic agglutination test (MAT, previously known as the agglutination-lysis test) or ELISAs. The MAT test is serogroup but not serovar specific, and can be complicated by cross-reactions. Less commonly used tests include complement fixation, radioimmunoassay, immunofluorescence, counterimmunoelectrophoresis and thin layer immunoassay. The macroscopic slide agglutination test may be used for a presumptive diagnosis, but is not specific. A high titer with consistent symptoms is suggestive of an acute case, but a rising titer is necessary for a definitive diagnosis. Few serovar-specific assays are available in human medicine.

Treatment

Severe leptospirosis is treated with antibiotics. The use of antibiotics for the mild form of disease is controversial, and the research is still inconclusive. Antibiotics used in humans include doxycycline, ampicillin, amoxicillin, penicillin and erythromycin. Supportive treatment and management of complications such as renal failure, hepatic complications, hemorrhages and CNS disease may also be necessary.

Prevention

The control of infections in livestock and pets reduces the risk of human disease, but the existence of wildlife reservoirs complicates prevention. Rodent control can be important in preventing human infections, particularly in urban areas.

Avoidance of contact with contaminated or potentially contaminated bodies of water can decrease the risk of infection. Domestic animals should not be allowed to urinate in water that humans contact. Draining wet areas may also decrease the incidence of disease. Food should also be protected from sources of infection.

Personal hygiene and protective clothing are important preventative measures in high risk occupations. Gloves and face shields can help prevent infections when working with infected animals or tissues. Rubber boots can decrease the risk of infection in sewer workers and agricultural workers who may wade in urine-contaminated water.

Human vaccines are available for workers in high risk professions in some countries but are not used in the U.S. Immunization is relatively serovar specific, and protects only against the serovar(s) in the vaccine or closely related serovars. Yearly vaccination is required and side effects, including painful swelling, can be seen.

Doxycycline has been used for short term prophylaxis.

Morbidity and Mortality

Leptospirosis has not been a notifiable disease in the U.S. since 1994, and the current incidence in humans is not known with certainty. From 1987 to 1993, 43-93 cases were reported annually. Currently, the U.S. Centers for Disease Control and Prevention (CDC) estimates that 100 to 200 cases are identified in the U.S. each year. Leptospirosis is thought to be underdiagnosed and underreported since many cases are mild or asymptomatic and self-limiting.

The incidence of infection is seasonal, with most cases seen during in the summer and fall in temperate regions. In tropical climates, the peak incidence occurs during the rainy season. Large outbreaks have been seen after floods.

Occupational exposure is thought to be responsible for 30-50% of cases. Occupations with a high risk of infection include sewer workers, coal miners, plumbers, farm workers, veterinarians, pet shop owners, abattoir workers, meat handlers, slaughterhouse workers, workers in the fishing industry, and the military. From 8-29% of those who work with livestock have antibodies to *Leptospira*. Recreational activities that increase the risk of leptospirosis include gardening and water sports such as canoeing, swimming and white-water rafting. Residents of some urban areas are exposed via rat urine.

Most cases of leptospirosis are asymptomatic or mild. The overall case fatality rate is 1-5%. The mortality rate varies with the form, and is higher in the elderly. The anicteric form is rarely fatal. The icteric form, which occurs in 5-10% of all patients, has an overall mortality rate of 5-15%, and a 54% case fatality rate in severe cases with myocardial involvement. Most patients with kidney failure, hepatic disease or anterior uveitis eventually recover kidney or liver function, and full vision.

Infections in Animals

Species Affected

All mammals appear to be susceptible to at least one species of *Leptospira*. Disease is rare in cats, and less common in sheep than cattle.

- Serovars associated with disease in cattle include *hardjo*, *pomona*, *grippotyphosa*, *canicola* and *icterohaemorrhagiae.*
- Serovars associated with disease in sheep and goats include *hardjo*, *pomona, grippotyphosa* and *ballum.*
- Serovars associated with disease in pigs include pomona, grippotyphosa, bratislava, canicola, icterohaemorrhagiae, tarassovi and muenchen.
- Serovars associated with disease in horses include *hardjo*, *pomona*, *canicola*, *icterohaemorrhagiae* and *sejroe.*
- Serovars associated with disease in dogs include *pomona, grippotyphosa, canicola, icterohaemorrhagiae, pyrogenes, paidjan, tarassovi, ballum* and *bratislava*.

The primary reservoir hosts for most *Leptospira* serovars are wild mammals, particularly rodents. Reservoir hosts among domestic animals include cattle, pigs, sheep and dogs. The specific reservoir host(s) vary with the serovar and the geographic region. Disease in reservoir hosts is more likely to be asymptomatic, mild or chronic. Reservoir hosts include:

- Rats: serogroups *icterohaemorrhagiae* and *ballum*
- Mice: serogroup *ballum*
- Cattle: serovars *hardjo*, *grippotyphosa* and *pomona*
- Sheep: serovars *hardjo* and *pomona*
- Pigs: serovars *pomona, tarassovi* and *bratislava*
- Dogs: serovars *canicola* and *bataviae*

Incubation Period

The incubation period is 4 to 12 days in dogs. Abortions usually occur 3 to 10 weeks after infection in cattle, and 15 to 30 days after infection in pigs.

Clinical Signs

Leptospira infections may be asymptomatic, mild or severe, and acute or chronic. The clinical signs are often related to kidney disease, liver disease or reproductive dysfunction. Chronically infected animals are often asymptomatic.

Cattle

Acute leptospirosis occurs mainly in calves. The symptoms may include fever, anorexia, conjunctivitis and diarrhea. Severely affected animals may also develop jaundice, hemoglobinuria, anemia, pneumonia, or signs of meningitis such as incoordination, salivation and muscle rigidity. Some calves may die within 3 to 5 days, and the survivors can be unthrifty after recovery. The clinical signs vary with the serovar: infections with serovar *hardjo*, for example, are not usually associated with hemolytic anemia.

In adult cattle, the early symptoms such as fever and depression are often transient and milder, and may go unnoticed. The most prominent signs of infection are abortions, decreased fertility or decreased milk yield. Some serovars cause late term abortions, stillbirths and increased neonatal mortality. The placenta is retained in up to 20% of the cows that abort, and infertility may be a sequela. Some serovars can cause sudden agalactia or decreased milk production. The milk may be thick, yellow, and blood-tinged but there is typically little evidence of mammary inflammation. The appearance of the milk usually improves in 4 to 5 days, and milk production returns to normal after 10 to 21 days. Jaundice may be seen in severely affected animals.

Sheep and goats

Leptospirosis in sheep and goats is similar to the disease in cattle. It is characterized by fever and anorexia and, in some animals, jaundice, hemoglobinuria or anemia. Abortions, stillbirths, weak lambs or kids and infertility can also be seen, either with or without other clinical signs. Clinical disease is relatively uncommon in sheep.

Swine

In swine, clinical leptospirosis is most often characterized by reproductive signs including late term abortions, infertility, stillbirths, mummified or macerated fetuses, and increased neonatal mortality. Fever, decreased milk production and jaundice may also be seen. In some infected herds, the only sign of infection may be a transient fever. Subclinical infections are common.

In piglets, there may be fever, anorexia, depression, diarrhea, jaundice, hemoglobinuria and gastrointestinal disorders, as well as signs of meningitis. Affected piglets may grow more slowly than normal, and high mortality rates can be seen in young or weak piglets.

Horses

Many infections in horses are subclinical. Ocular disease is the most common syndrome. During the acute phase, ocular signs may include fever, photophobia, conjunctivitis, miosis and iritis. Corneal opacity and periodic ophthalmia may be sequelae of acute infections. In the chronic phase, there may be anterior and posterior adhesions of the eye, a turbid vitreous body, cataracts, uveitis and other ocular abnormalities.

Although systemic disease is uncommon, severe cases of leptospirosis accompanied by liver, kidney or cardiovascular disease have been described. Recently, leptospirosis has also been associated with a number of abortions.

Dogs

The clinical signs and severity of disease are highly variable in dogs. Some infections are asymptomatic or mild, while others are severe or fatal. The initial signs are usually nonspecific and may include fever, depression, anorexia, stiffness, myalgia, shivering and weakness. The mucus membranes are often injected. These symptoms may be followed by signs of kidney disease including anuria, hematuria or increased frequency of urination, vomiting, dehydration and oral ulceration. Abortions, diarrhea, gray stools, coughing, dyspnea, conjunctivitis, weight loss and jaundice may also be seen. Hemorrhagic syndromes occur in some dogs: the mucus membranes may have widespread petechial and ecchymotic hemorrhages and, in later stages of the disease, there may be hemorrhagic gastroeneteritis and epistaxis. Some dogs die peracutely without clinical signs. Chronic kidney disease can be a sequela.

Chronic infections may be asymptomatic, or associated with fever of unknown origin and conjunctivitis.

Some serovars are more likely to cause certain syndromes. Fever, hemorrhage, anemia and jaundice are typically associated with the serovar *icterohaemorrhagiae*. Serovar *grippotyphosa* tends to cause severe acute kidney failure and/or chronic active hepatitis Dogs infected with serovar *pomona* are often asymptomatic and chronic carriers Serovar *canicola* often causes chronic interstitial nephritis.

Wild animals

Infections are often asymptomatic in wild animals, including rodents.

Seals

Symptoms reported in seals and sea lions have included depression, polydipsia, fever, abortions and neonatal deaths.

Communicability

Leptospira spp. are shed in the urine of acutely infected animals. Chronic carriers may excrete them for months or years. In addition, organisms can be found in aborted or stillborn fetuses, as well as in normal fetuses or vaginal discharges after calving. Rarely, *Leptospira* is transmitted through rodent bites.

Diagnostic Tests

Leptospirosis can be diagnosed by culture, detection of antigens or nucleic acids, or serology. The location of the organisms varies with the form of the disease. In acute infections, *Leptospira* may be found in the blood, milk, and cerebrospinal, thoracic or peritoneal fluids. During chronic infections, they are sometimes found in the urine. The liver,

lung, brain and kidney are collected at necropsy from acute cases, and the kidney and genital tract are tested in chronic cases. Organisms can also be found in the body fluids or tissues of aborted fetuses.

Leptospira species can be cultured on a variety of media but are fastidious and grow slowly on primary isolation. Special transport media may be required for shipment to the laboratory. Depending on the serovar, culture may take up to 13 to 26 weeks. Identification to the species, serogroup and serovar level is done by reference laboratories, using genetic and immunologic techniques. *Leptospira* can also be identified in clinical samples by immunofluorescence and immunhistochemical staining, as well as DNA probes and polymerase chain reaction (PCR) techniques. Darkfield microscopy can be used but is non-specific. Silver staining is sometimes useful as an adjunct technique. These organisms stain poorly with the Gram stain. Antigen-detection techniques including ELISAs and radioimmunoassay have been reported in the literature.

Serology is also used for diagnosis. Paired acute and convalescent samples are preferred from most animals, but a single positive sample from an aborted fetus is diagnostic. Herd tests are often used in ruminants. The most commonly used serological tests are the microscopic agglutination test (MAT) and enzyme-linked immunosorbent assays (ELISAs). Serovar-specific ELISAs are available in veterinary medicine, and cross-reactions are less common in animals than in humans. Other serologic tests include radioimmunoassay, the microcapsule agglutination test, immunofluorescence, counterimmunoelectrophoresis and thin-layer immunoassay. A milk ELISA can detect antibodies in samples from individual cows or in bulk milk. Titers may become undetectable in chronically infected dogs that are still shedding organisms.

Treatment

Antibiotics used to treat leptospirosis include the tetracyclines, penicillin/ampicillin, dihydrostreptomycin, streptomycin and the fluoroquinolones. The efficacy of treatment may depend on the serovar. Fluid therapy, blood transfusions and other supportive care may also be necessary.

In beef herds, further abortions may be prevented by vaccination and treatment of all animals with antibiotics, if leptospirosis is diagnosed early during an outbreak. In dairy cattle, only infected animals are usually treated, due to the potential loss of milk sales.

Prevention

Leptospirosis vaccines are available for pigs, cattle and dogs. Although the vaccines prevent disease, they do not completely prevent infection or the shedding of the organisms. Immunity is largely serovar specific: vaccines are protective only against the included serovars or closely related serovars. Prophylactic treatment of exposed animals with antibiotics can also prevent disease.

Sanitation and the prevention of contact with contaminated environments or infected wildlife, particularly rodents, can decrease the risk of infection. Animals should not be allowed to drink from or enter contaminated bodies of water. Good sanitation can reduce the risk of infection in kennels, and in areas where livestock are bred or give birth.

In cattle, infections are usually introduced in an infected animal, through the environment, or by contact with infected sheep or pigs. Replacement stock should be selected from herds negative for leptospirosis. Animals not known to be *Leptospira*-free should be quarantined for 4 weeks and tested before being added to the herd. Other control measures include vaccination, isolation and treatment of infected animals, rodent control, prevention of contact with wildlife, sheep and pigs, and prevention of access to contaminated bodies of water. Vaccination and management, including the separation of young cattle from older animals, can eradicate leptospirosis from a herd over a period of years. Eradication has also been accomplished in closed herds by vaccination and testing over a five-year period. Similar measures can help to prevent or control leptospirosis in pigs and sheep.

Morbidity and Mortality

Leptospirosis is particularly prevalent in warm and humid climates, marshy or wet areas, and in regions with an alkaline soil pH. This disease is often seasonal: it is most common during the rainy season in the tropics, and in the summer and fall in temperate regions.

In newly infected cattle herds, up to 30% of the cows may abort, and overall calf production can decrease by up to 40%. In endemically infected herds, abortions are usually sporadic and occur mainly in younger animals. Infertility, with decreased pregnancy rates and increased culling, may also be noted. The estimated decrease in the first service conception rate is approximately 16-32%. Deaths can occur in calves; however, maternal antibodies are protective for up to 6 months.

Similarly, leptospirosis is often asymptomatic or mild in adult pigs, and reproductive signs are the main evidence of infection. High mortality rates may be seen in young or weak piglets.

In dogs, the risk of infection is highest in hunting dogs, show dogs and dogs with access to water such as ponds. The severity of disease is affected by the dog's age, previous leptospirosis vaccinations and the serovar, route of exposure, and dose of organisms. Most treated dogs recover after 2 weeks, but severe kidney or liver damage can be fatal. The case fatality rate is approximately 10% in this species.

Post-Mortem Lesions

Cattle

In acute cases, there may be signs of anemia, as well as icterus, hemoglobinuria, and submucosal and subserosal

hemorrhages. The kidneys are typically swollen and contain petechiae and ecchymoses, which become pale over time. The liver is sometimes swollen, with minute foci of necrosis. Ulcers and hemorrhages may be found in the mucosa of the abomasum. Petechiae can also be seen in other organs in some fulminating infections. Pulmonary edema and emphysema are rare but have been reported.

Dogs

In acute infections, the kidneys and/or liver can be swollen, and hemorrhages may be found in any organ. Lesions associated with acute uremia may also be seen. In chronically infected dogs, there may be gray or white foci and/or streaks in the kidney and liver.

Seals

Severe interstitial nephritis and gastroenteritis have been reported in infected seals. Hepatitis may not be grossly apparent but the gall bladder may contain inspissated black bile.

Internet Resources

Animal Health Australia. The National Animal Health Information System (NAHIS)
http://www.aahc.com.au/nahis/disease/dislist.asp

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/ncidod/diseases/submenus/sub_lepto.htm

eMedicine.com. Leptospirosis
http://www.emedicine.com/emerg/topic856.htm

FAO Manual on Meat Inspection for Developing Countries
http://www.fao.org/docrep/003/t0756e/t0756e00.htm

International Veterinary Information Service (IVIS)
http://www.ivis.org

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/eng/normes/mmanual/a_summry.htm

Material Safety Data Sheets –Canadian Laboratory Center for Disease Control
http://www.hc-sc.gc.ca/pphb-dgspsp/msds-ftss/index.html#menu

Medical Microbiology
http://www.gsbs.utmb.edu/microbook

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com/mvm/index.jsp

Organic Livestock Research Group, The University of Reading
http://www.organic-vet.reading.ac.uk

World Organization for Animal Health (OIE)
http://www.oie.int/

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