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Public Health

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LEPTOSPIROSIS

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Introduction

Leptospirosis is a zoonotic disease due to infection by bacteria of the genus *Leptospira*. Leptospires are thin, flexible, finely coiled, Gram-negative bacteria. In darkfield microscopy they show up as mobile bacteria with axial flagella, one at each end. Leptospires are obligately aerobic, slow growing, and require long-chain fatty acids or long-chain alcohols as a primary energy source.

The genus *Leptospira* is subdivided into 20 genomospecies based on DNA-DNA hybridization. Of these, nine are classified as pathogenic to humans, five are intermediate or opportunist, and six are saprophytic (non-pathogenic). More important to clinicians and epidemiologists is the serological classification as severity of infection and specific animal reservoirs vary between the genus' serovars. Serologically, *Leptospira* is subdivided into 26 serogroups which are made up of approximately 300 antigenically defined serovars, more than 200 of which are known to be pathogenic. Approximately half of all pathogenic serovars belong to the genomospecies *L. interoggans* and *L. borgpetersenii*.

Epidemiology

Environments, Reservoirs, and Transmission Characteristics

Leptospirosis is found throughout the world, but is thought to be most prevalent in tropical regions where conditions allow leptospires to persist in the soil for longer periods of time, increasing the chance of transmission to other animals and humans. Ideal conditions for leptospires in the environment follow a seasonal pattern and include fresh water, damp alkaline soil, vegetation, and mud, conditions coinciding with both the rainy seasons and fall in much of the world. Spikes in disease incidence have also been reported following natural disasters involving exposure to heavy rainfalls and/or flooding like hurricanes and monsoons.

Leptospirosis is a common infection of amphibians, reptiles, and mammals. Infected animals may become reservoirs when leptospires persist in immunologically privileged sites, in particular, the renal tubule. It is not uncommon for infected opossums, skunks, raccoons, and foxes to shed leptospires in their urine 10% to 50% of the time. Leptospires, excreted in animal urine, placenta and amniotic fluid, become established in soil and water where they can survive for weeks to months.

Humans and other animals become infected after contact with soil or water or after direct contact with infected animal tissues and organs. Leptospirosis has a medium-length incubation period averaging five to 14 days with a range from two to 30 days. Transmission occurs through cuts; abraded and softened, waterlogged skin; mucous membranes or conjunctivae; aerosol inhalation of microscopic droplets; and possibly ingestion. Because humans are rarely chronic carriers, they are considered accidental hosts. Pet dogs and rats are likely to play an important role in the peridomestic amplification and transmission of infection. Humans with leptospirosis usually excrete the organism in the urine for four to six weeks and occasionally for as long as 18 weeks. Person-to-person transmission is rare.

Leptospirosis is commonly seen as an occupational hazard to rice and sugarcane field workers, farmers, crawfish farmers, sewer workers, animal husbandry workers, veterinarians, dairy workers, abattoir workers and outdoors people such as campers, bathers and sportsmen exposed to contaminated rivers, canals or lake waters.

Disease Burden

Worldwide, an estimated 868,000 people are currently infected with leptospirosis with close to 50,000 deaths occurring each year. Some tropical regions in particular are estimated to have endemic-levels of the disease with as much as 80% of the population having a positive seroconversion rate, indicating a past or present infection. Regions with the highest estimated rates of leptospirosis include: the Caribbean islands, Central and South America, Southeast Asia, and the Pacific islands.

In the U.S., an estimated 100 to 200 cases occur every year, with approximately half occurring in Hawaii. Between 1994 and 2013, Leptospirosis ceased to be a nationally reportable disease due to very low case counts and unreliable diagnostic testing paired with a lack of efficient transmission control practices. However, many states, including Louisiana, continued to collect and report surveillance data. In Louisiana, between 1987 and 2014, the range of annual cases (hospitalized, reported, or both) each year has been one to six cases with an average of just under three cases per annum.

Epidemics of leptospirosis have occurred after investigations of unexplained febrile illness associated with flooding, tropical storms, and hurricanes in the Caribbean and Central and South America. Heavy rains resulting from such natural disasters increase human exposure to leptospire-contaminated groundwater and soil and may also facilitate peridomestic rodent infestation resulting in transmission to humans. Walking through streams, creeks, and puddles and observing rodents in food preparation areas were the predominant risk factors associated with disease after these natural disasters.

Clinical Description

Wild, domestic, or peridomestic animal infections, such as those occurring in rodents, livestock, and dogs, range from subclinical to symptomatic (e.g., listlessness, anorexia, and abortion).

Leptospira infections range from subclinical illness detected by seroconversion among persons with frequent exposure to severe illness. There are four disease presentations seen in patients experiencing clinical infections:

1. The acute or leptospiremic phase
2. Weil's Syndrome (arguably the most severe form of infection)
3. Leptospirosis Associated Pulmonary Hemorrhage Syndrome
4. Aseptic meningitis

• A severe, potentially fatal illness starting with fever, chills, myalgias (usually calf and lumbar regions), and headache, and may include conjunctivitis, abdominal pain, vomiting, diarrhea, and skin rashes. It rapidly becomes complicated by any combination of renal failure, liver failure, and pneumonitis with hemorrhagic diathesis. An acute septicemic phase can be followed by a secondary (immune) phase of severe disease characterized by aseptic meningitis, jaundice, renal failure, and hemorrhage; the disease sometimes can progress rapidly to acute respiratory distress syndrome. Weil's disease, characterized by impaired hepatic and renal function, is but one form of severe illness that may develop after the acute phase of illness.

• Aseptic meningitis, with or without symptoms, is characteristic of the immune phase of illness, occurring in up to 80% of patients. Symptomatic patients present with an intense, bitemporal and frontal throbbing headache with or without delirium. A lymphocytic pleocytosis occurs with total cell counts generally below 500/mm^3. CSF protein levels are modestly elevated between 50 and

100mg/ml; the CSF glucose concentration is normal. Rarely, severe neurologic disturbances including coma, hemiplegia, and transverse myelitis occur.

Laboratory Tests

Darkfield microscopy may provide a presumptive diagnosis of leptospirosis in experienced hands. However, false-negative and false-positive examinations are frequent due to the low concentration of organisms (even after centrifugation) and the presence of fibrin and other filamentous cellular extrusions found in most body fluids. Immunohistochemical techniques using immunoalkaline phosphatase and/or immunoperoxidase staining methods can readily detect leptospiral antigens and intact leptospires in infected tissue specimens.

Leptospires can be recovered from blood, CSF, and most tissues during the acute phase of illness (first seven to10 days following symptom onset). After five to seven days of illness, leptospires may also be recovered from urine for up to 14 days or more after symptom onset. Isolation can be difficult and can require up to 16 weeks even in experienced laboratories. In addition, the sensitivity of culture for diagnosis is considered to be low.

Molecular methods including randomly amplified polymorphic DNA fingerprinting, or PCR-restriction endonuclease analysis are performed at CDC laboratories.

The final identification of leptospiral isolates to the serovar level is performed by the microscopic agglutination test (MAT), using reference rabbit antisera raised against the type serovars of all recognized serogroups. The CDC reference laboratory uses a standard panel of 23 antigens representing 21 serovars and 17 serogroups, supplemented with additional serovars as needed. Serial dilutions of serum in phosphate-buffered saline are added to wells containing live antigen, incubated, and read to the end-point defined as the highest dilution that agglutinates 50% or more of leptospires visualized at 100× by darkfield microscopy. A serologically confirmed case of leptospirosis is defined by a four-fold rise in MAT titer to one or more serovars between acute-phase and convalescent serum specimens run in parallel. A titer of at least 1:800 in the presence of compatible symptoms is strong evidence of recent or current infection. Suggestive evidence for recent or current infection includes a single titer of at least 1:200 obtained after the onset of symptoms, or a titer of at least 1:100 on consecutive specimens. Delayed seroconversions are common, with up to 10% of patients failing to seroconvert within 30 days of the clinical onset. Cross-reactive antibodies may be associated with syphilis, relapsing fever, Lyme disease, and legionellosis.

Collect one red-topped tube of venous blood for each specimen. The blood should either be spun down and the sera sent or the whole blood sent refrigerated.

Alternative, more rapid serologic tests including an indirect hemagglutinin assay (IHA) and several recently developed IgM indirect enzyme-linked immunosorbent assays (ELISAs) are available, but these tests lack the ability to provide information about the serogroup or serogroups most likely to be responsible for disease.

Recently a rapid dipstick test for the serodiagnosis of human leptospirosis was developed. The test is simply performed by incubation of a dipstick in a mixture of serum and detection reagent. At the end of the incubation the dipstick is rinsed with tapwater and the result can be viewed directly with the naked eye. In 3000 serum samples tested, sensitivity and specificity were well over 90%. The sensitivity, however, depends on the stage of the disease and is lower during the first five to seven days after the onset of the disease).

Treatment

Mild infections can be treated with oral doxycycline; more severe infections generally require intravenous penicillin.

Surveillance

In 1995, leptospirosis was removed from the national list of notifiable diseases, primarily due to the small number of cases detected through passive surveillance. However, as of January 2013, it has been reinstated as a national notifiable disease.

Case Definition

Clinical description

An illness characterized by fever, headache, chills, myalgia, conjunctival suffusion, and less frequently by meningitis, rash, jaundice, or renal insufficiency. Symptoms may be biphasic.

Clinical Criteria for Diagnosis

History of fever paired with:

- At least two of the following: headache; chills; myalgia; conjunctival suffusion; meningitis; rash; jaundice; or renal insufficiency.

OR

- At least one of the following: aseptic meningitis; GI symptoms; pulmonary complications; cardiac arrhythmias/ECG abnormalities; renal insufficiency; hemorrhage; or jaundice with acute renal failure.

Laboratory criteria for diagnosis

Confirmed:

- Isolation of *Leptospira* from a clinical specimen

OR

- Fourfold or greater increase in *Leptospira* agglutination titer between acute- and convalescent-phase serum specimens obtained greater than or equal to two weeks apart and studied at the same laboratory

OR

- Demonstration of *Leptospira* in a clinical specimen by immunofluorescence

OR

- *Leptospira* agglutination titer of ≥ 800 by Microscopic Agglutination Test (MAT) in one or more serum specimens

OR

- Detection of pathogenic *Leptospira* DNA (e.g., by PCR) from a clinical specimen

Supportive:

- *Leptospira* agglutination titer of ≥ 200 but < 800 by Microscopic Agglutination Test (MAT) in one or more serum specimens

OR

- Demonstration of anti-*Leptospira* antibodies in a clinical specimen by indirect immunofluorescence

OR

- Demonstration of *Leptospira* in a clinical specimen by dark field microscopy

OR

- Detection of IgM antibodies against *Leptospira* in an in acute phase serum specimen

Epidemiologic Linkage

- Involvement in an exposure event (e.g., adventure race, triathlon, flooding) with associated laboratory-confirmed cases

Case classification

Confirmed: A case with confirmatory laboratory results, as listed above.

Probable: A clinically compatible case with at least one of the following:

- Epidemiologic linkage with known cases

OR

- Supportive laboratory findings, but without confirmatory laboratory evidence of *Leptospira* infection

Investigation

The purpose of investigation is to identify cases, to identify the source of infection, and to institute control measures when possible to minimize disease transmission.

If an outbreak is suspected:

- Contact the physician and/or hospital to confirm the diagnosis
- Obtain appropriate laboratory specimens
- Search for source of infection; eliminate the contamination or prohibit use

Prophylaxis

Several studies including a double-blind placebo-controlled efficacy trial of doxycycline conducted among two military units deployed on a three-week jungle training exercise have demonstrated the efficacy of pre-exposure chemoprophylaxis on clinical symptoms and mortality attributed to leptospirosis, using oral doxycycline at 200 mg once a week (95% efficacy). Persons traveling to areas where leptospirosis is endemic or epidemic and who participate in high-risk exposure activities are at increased risk for leptospirosis and may benefit from pre-exposure chemoprophylaxis.

Doxycycline chemoprophylaxis may also be recommended for travelers participating in high-risk water sport activities in known endemic areas, as well as for persons living or working in highly endemic areas after natural disasters resulting in heavy rainfall and flooding.

Prevention of transmission

- Protective clothing, boots, and gloves should be worn for occupational exposure.
- Vaccination of dogs and livestock prevents disease but not necessarily infection and renal shedding.
- Rodent control is indicated.
- Reducing both direct contact with infected animals and indirect contact with animal urine-contaminated fresh water, soil and mud is the most effective prevention strategy available.

- Maintaining careful hygienic practices within and around farmyards and abattoirs is encouraged. Flat surfaces should be washed down regularly with sodium hypochlorite (1:4000) or other detergents to kill leptospires.

- Although difficult to achieve, rodent pest control after heavy rains in known endemic areas may be useful. Decontamination of large bodies of leptospire-contaminated fresh water is, generally speaking, impractical

Hospital precaution and isolation: Standard precautions