CHAPTER 23

Leptospirosis

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Leptospirosis is the commonest zoonosis worldwide. It occurs in all areas except polar regions and is particularly common in the tropics and subtropics. Typical cases present abruptly with high fever and chills, intense headache, severe myalgias, and conjunctival suffusion. Many cases have a nonspecific presentation, however, and are often misdiagnosed. Adventurous travelers, especially to tropical and subtropical regions, are at increased risk of leptospirosis and should be identified and counseled appropriately prior to departure. The diagnosis of leptospirosis is fraught with problems. A combined approach using culture (blood, urine, cerebrospinal fluid [CSF]) plus serology (acute and convalescent sera) is recommended in order to help make the diagnosis. If available, polymerase chain reaction (PCR) may provide rapid, early diagnosis. Appropriate antibiotic treatment should be started as soon as possible after the diagnosis is suspected.

ETIOLOGY

Leptospirosis is caused by an aerobic, tightly coiled, highly motile spirochete with hooked ends measuring 0.1 μm in diameter and from 6 to 20 μm in length. Because the organism is slender and highly motile, it is capable of passing through membrane filters 0.2 μm in diameter. This may be an important consideration for anyone planning to use water filters to purify their drinking water. The organism survives best in moist, warm conditions (optimal temperature 28-30° C) in a slightly alkaline environment (optimal pH 7.2-7.4). The genus *Leptospira* includes two species: *L. interrogans*, which is pathogenic, and *L. biflexa*, which is saprophytic and nonpathogenic. *L. interrogans* is divided into 23 serogroups and more than 200 serovars, most of which can cause infections in humans. Serovars from common serogroups that cause infection in humans include *australis*, *ballium*, *canicola*, *grippotyphosa*, *hardjo*, *hebdomadis*, *icterohaemorrhagiae*, and *pomona*.

EPIDEMIOLOGY

Leptospirosis occurs worldwide, except in polar regions. Human infection may be epidemic, sporadic, or endemic. Leptospirosis is most common in warm, moist, tropical and subtropical regions, especially areas that have heavy rainfall and neutral or alkaline soil. Infection is often seen in agricultural areas with large numbers of livestock or rodents or in areas with large wildlife populations. It is most common in the rainy season in the tropics and in the summer and fall in temperate climates, probably reflecting the increased opportunity for exposure to contaminated fresh water. Outbreaks of leptospirosis may be a serious threat after severe flooding.

Leptospirosis is a zoonosis with many wild and domestic animal reservoirs, including rats, mice, mongooses, pigs, dogs, and cattle. The cycle of transmission is shown in **Figure 23.1**. Following infection, animals often harbor leptospira in the kidneys. The organism multiplies and may be shed in the urine for months or years. Infected animals are often asymptomatic.

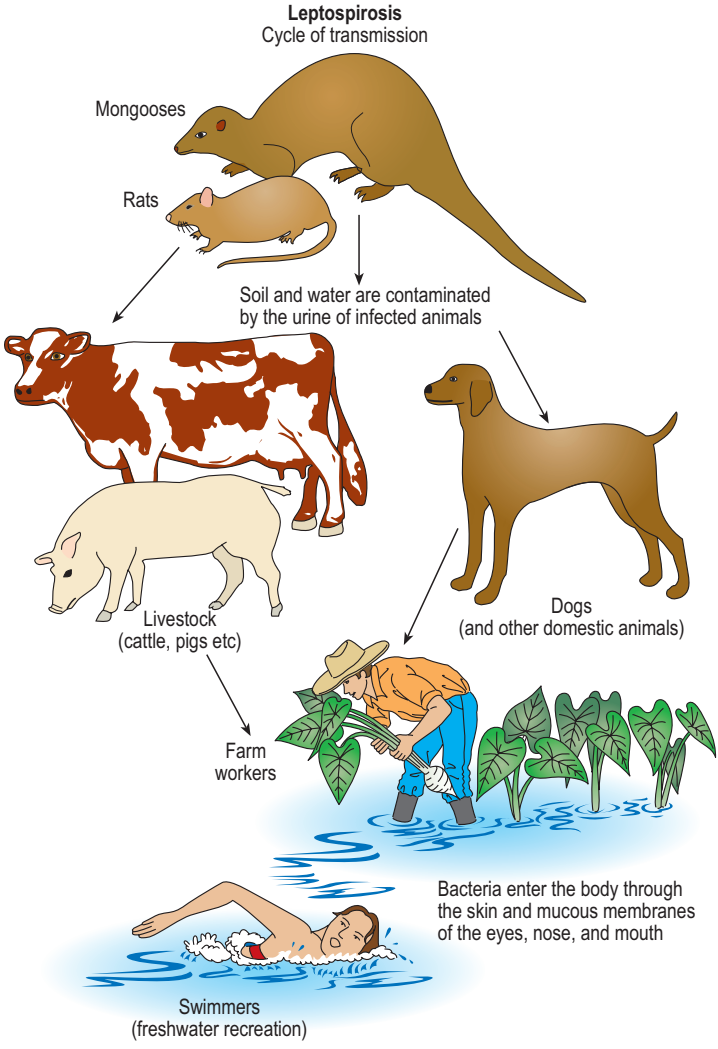

Fig. 23.1 Cycle of transmission of leptospirosis from animal to man. (From the Hawaii Department of Health.)

Leptospira proliferate in fresh water, damp soil, vegetation, and mud. Humans become infected by exposure to infected animal urine either by direct contact or as the result of indirect exposure through contaminated water or moist soil. Indirect contact is the commonest source of infection and may occur via contaminated mud or fresh water in rivers, lakes, and streams. It occurs in a wide variety of occupational (e.g., rice or sugar cane farmers, sewage workers, or miners) and recreational (e.g., rafting, hiking, swimming, fishing, or gardening) situations. Direct contact with contaminated urine and tissues of

infected animals may occur in hunters, dairy or cattle farmers, abattoir workers, or veterinarians. Infection is acquired through damaged skin, for example, cuts and abrasions, or via exposed mucous membranes of the nose, mouth, and eyes. Very rarely, infection may be the result of laboratory accidents, animal bites (contaminated with urine), blood transfusions, organ transplants, ingestion of breast milk, sexual intercourse, or congenital transmission.

High antibody prevalence rates have been reported from many tropical and sub-tropical countries. Examples include Belize 37%, Tahiti 30%, Thailand 27%, and Vietnam 23%. Average annual incidence rates in tropical and subtropical countries are also high, for example, Tahiti 20/100,000 and Barbados 123/100,000. In contrast, the average annual incidence rate in the United States is 0.02/100,000. Typically, at least half the cases of leptospirosis diagnosed in the United States are from Hawaii, and average annual incidence rates on the island of Kauai may be as high as 24/100,000. Leptospirosis is commonest on the Hawaiian Islands that have the most rainfall (Kauai and Hawaii Island), especially in the windward (wetter) areas of those islands. Historically an occupational disease of sugar cane workers in Hawaii, leptospirosis has become increasingly recognized as a recreational disease in recent years.

Some serovars appear to be associated with particular animals. Examples include *icterohaemorrhagiae* (rats), *canicola* (dogs), *pomona* (swine), *autumnalis* (rats, raccoons), *hardjo* (cattle), and *bratislava* (swine, badgers).

It has been noted that outbreaks of leptospirosis often occur after periods of heavy rainfall and flooding. It is thought that rain washes the organism from the river banks into surface waters, while, at the same time, flooding results in increased human contact with water and forces infected animals into closer contact with humans. A major outbreak occurred after widespread flooding in Nicaragua in 1995 and was responsible for more than 2000 cases and more than 40 deaths. An outbreak in white-water rafters in Costa Rica in 1996 was also linked to heavy rainfall. In 1998, the largest outbreak in recorded U.S. history involved a group of tri-athletes who had swum in a lake after heavy rainfall in Illinois. A total of more than 60 cases were reported in this outbreak. A further example of the association of leptospirosis with flooding was in late 1998, in the aftermath of Hurricane Mitch, when outbreaks of leptospirosis were reported from various countries in Central America, including Honduras, Guatemala, and Nicaragua. In 2000 an important outbreak of leptospirosis occurred in participants of an "Eco-Challenge" multisport athletic event in Borneo following very heavy rainfall. More recently, outbreaks have been reported after flooding in urban slums of Brazil, India, and Thailand. In addition, many areas of the Philippines have experienced large outbreaks of leptospirosis following recent typhoons, prompting the government to provide antimicrobial prophylaxis with doxycycline to millions of people.

There have been many reports of leptospirosis in travelers, but despite this, the infection continues to be underrecognized in this group. With the increased popularity of recreational and wilderness activities in travelers, there is an increased risk of leptospirosis, particularly in tropical and subtropical regions. Travel medicine specialists should make special efforts to identify and counsel travelers at risk of leptospirosis. This is particularly important in travelers to areas that have experienced recent flooding, because they may be at increased risk of infection. In certain situations, prophylactic antibiotics may be indicated. It is also very important to consider the diagnosis of leptospirosis in a returned traveler who presents with appropriate exposure history and relevant clinical features. Clinicians who see returned travelers need to have a high index of suspicion for leptospirosis, particularly bearing in mind the potentially long incubation period of up to 30 days. Prompt clinical diagnosis is particularly important, because appropriate antibiotic treatment needs to be started early to maximize its benefit.

CLINICAL

The incubation period is usually 7-14 days but may range from 2 to 30 days. Over 90% of cases are relatively mild and self-limited. The remaining cases may be severe, often associated with jaundice and potentially life-threatening, sometimes referred to as Weil syndrome

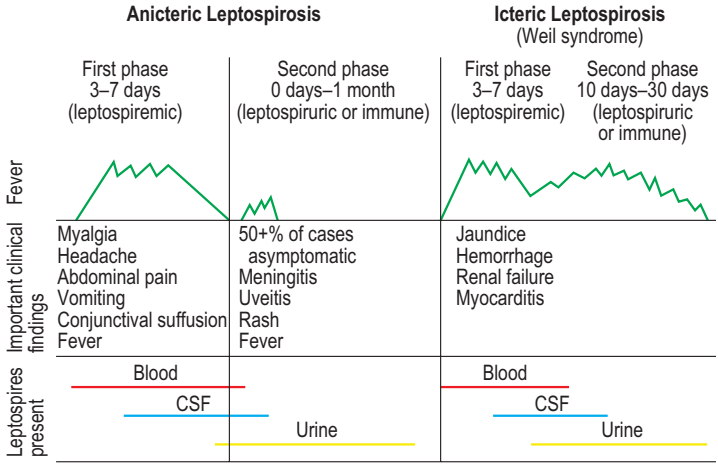

Fig. 23.2 The clinical course of leptospirosis: anicteric and icteric disease. *CSF*, Cerebrospinal fluid. (Adapted from: Feigin, R.D., Anderson, D.C., 1998. Leptospirosis. In: Feigin, R.D., Cherry, J.D. (Eds.), Textbook of Pediatric Infectious Diseases, fourth ed, vol. 2. Saunders, Philadelphia.)

(named after Adolf Weil, who was the first to describe the severe form of leptospirosis in 1892). Totally asymptomatic infections are probably rare.

The illness may be biphasic. The first, or "leptospiremic," phase typically lasts 3-7 days and represents the period when organisms are present in the blood. The second ("leptospiruric"), or immune phase, may be clinically silent or last for up to 1 month or longer. It coincides with the formation of circulating IgM antibodies. In the commoner, milder (anicteric) form of leptospirosis, there may be a clinically apparent, symptom-free interval of 1-3 days between the first and second phases (**Fig. 23.2**).

Anicteric Leptospirosis

Leptospirosis has protean manifestations. The classic presentation is with fever, headache, myalgias, and conjunctional suffusion. Typically, the onset is abrupt with high fever (often >39°C), chills, and a severe frontal headache. Patients may report that this is the worst headache they have ever experienced. Muscle pain and tenderness is common and typically involves the muscles of the calves, thighs, and lower back. Conjunctival suffusion (dilatation of conjunctival vessels without inflammation, not conjunctivitis) is virtually pathognomonic of leptospirosis when observed. It usually appears on the third or fourth day of illness and is probably very common, although it may be mild and easily overlooked if not sought diligently. Large studies have shown a prevalence of anywhere from 8 to 100%. Subconjunctival hemorrhages are often present.

Gastrointestinal symptoms may include abdominal pain, nausea, vomiting, and diarrhea. Pulmonary involvement occurs in 20-70% of cases. Respiratory symptoms may include cough, sometimes with hemoptysis, dyspnea, chest pain, and sore throat. Rashes are present in 10-30% of patients during the first week of illness, but typically last only 1-2 days. They may be erythematous, macular, maculopapular, urticarial, petechial, or purpuric.

There may be a symptom-free period of 1-3 days followed by the second (leptospiruric), or immune phase. This is often clinically inapparent. The hallmark of this phase is aseptic meningitis, and symptoms include headaches, neck stiffness, nausea, vomiting, and photophobia. There may be a low-grade temperature. Rashes may also be present during this phase. Inflammation of the anterior uveal tract has been reported in 2-10% of patients. It

presents clinically as iritis, iridocyclitis, or chorioretinitis several weeks or months after the initial illness. It is usually bilateral and may run a prolonged or recurrent course. Rarely, long-term neuropsychiatric changes such as headaches, inability to concentrate, mood swings, depression, and psychosis have been reported following infection.

Severe (Icteric) Leptospirosis (Weil Syndrome)

Approximately 10% of patients with leptospirosis develop a severe, potentially life-threatening form of the disease. The onset of illness is indistinguishable from the milder form of leptospirosis. After 4-9 days, however, there is progression to a severe illness characterized by complications such as jaundice, renal failure, hemorrhage, and cardiopulmonary insufficiency or failure. Jaundice usually appears between the fifth and ninth days of illness and may last for several weeks. It may be marked, but liver failure is rare, because severe hepatocellular damage is very unusual. Tender hepatomegaly is common, and splenomegaly may occur. Renal involvement is common and may be evident within 3-4 days of onset. Several factors may be involved in the pathogenesis of renal insufficiency, including hypovolemia, hypotension, and acute tubular necrosis. Oliguric or non-oliguric renal failure usually occurs during the second week of illness. Peritoneal or hemodialysis may be required, although many cases can be managed without dialysis.

Hemorrhage appears to be the result of severe vasculitis, with endothelial damage resulting in capillary injury. Hemorrhagic manifestations include petechiae, purpura, bleeding gums, epistaxis, hemoptysis, gastrointestinal hemorrhage, and, rarely, subarachnoid or adrenal hemorrhage. Cardiac involvement may result in myocarditis or pericarditis, and there may be arrhythmias such as atrial fibrillation, atrial flutter, and a variety of conduction disturbances. Congestive heart failure may occur, and evidence of myocarditis is often present in fatal cases.

Pulmonary Leptospirosis

Pulmonary involvement may be prominent in severe leptospirosis. It may manifest as pulmonary hemorrhage, pneumonic consolidation, pleural effusions, or adult respiratory distress syndrome. Epidemics of leptospirosis with severe, sometimes fatal, pulmonary hemorrhage have been reported in Korea, China, Brazil, and Nicaragua. No single serovar was isolated in these cases. Typically, jaundice was rare or absent in these cases, distinguishing them from classic Weil syndrome and emphasizing that jaundice is not necessarily present in severe leptospirosis.

Overall mortality for leptospirosis is probably <1%. In severe leptospirosis, however, the mortality rate is about 5-10% and may be even higher in developing countries where facilities for dialysis and intensive care are often not readily available. Mortality tends to be particularly high in cases of pulmonary leptospirosis, in the elderly, or if there is serious underlying disease. Leptospirosis in pregnancy may be responsible for spontaneous abortion, particularly if infection occurs early in pregnancy. Congenital infection is probably rare.

DIFFERENTIAL DIAGNOSIS

Clinical manifestations of leptospirosis are very variable and often nonspecific. Clinicians should have a high index of suspicion to avoid misdiagnosis. There may be diagnostic clues or "red flags" that should alert clinicians to the possibility of leptospirosis (**Box 23.1**). There is often a broad differential diagnosis, particularly in a traveler who has recently returned from the tropics (**Box 23.2**). For example, leptospirosis may present as an unexplained febrile illness, pharyngitis, aseptic meningitis, or hemorrhagic fever, or it may mimic infections such as dengue fever, malaria, viral hepatitis, or typhus.

DIAGNOSIS

Cultures

Cultures should be obtained whenever possible, because they may aid in detecting cases that would be missed by serology alone. Blood and, where appropriate, CSF should be

Box 23.1 Diagnostic Red Flags

- History of contact with fresh water or mud
- History of contact with animals
- History of skin cuts or abrasions
- Abrupt onset of severe headache
- Severe myalgias (calves, thighs, lumbar area)
- Conjunctival suffusion
- Fever and new onset atrial fibrillation
- Jaundice with relatively mild transaminase elevation
- Fever, jaundice, and thrombocytopenia
- Hepatitis and neutrophil leukocytosis
- Fever and elevated creatine kinase levels
- Fever and elevated amylase levels

Box 23.2 Differential Diagnosis

- Influenza
- Streptococcal pharyngitis
- Viral hepatitis
- Aseptic meningitis
- Acute human immunodeficiency virus
- Legionnaires' disease
- Lyme disease
- Brucellosis
- Toxoplasmosis
- Hantaan virus
- Dengue fever
- Malaria
- Typhoid fever
- Rickettsial diseases (e.g., typhus, Q fever)
- Hemorrhagic fevers
- Relapsing fever
- Melioidosis
- Zika virus
- Chikungunya

cultured during the first 7-10 days of illness, prior to the administration of antibiotics. Urine should be cultured during the second week of illness and for up to 30 days after onset (**Fig. 23.2**). Tissue specimens and dialysis fluid can also be cultured in appropriate situations. Cultures should be inoculated as soon as possible using special media, for example, Fletcher semisolid or Tween 80-albumin (EMJH). Blood that cannot be inoculated immediately should be heparinized. If there is any delay in inoculating urine, it should be alkalinized

using bovine serum albumin. It is important to emphasize that cultures may take anywhere from 1 to 6 weeks to become positive.

Immunodiagnosis

IgM antibodies appear as early as 4 days after the onset of symptoms but are usually not demonstrable until the second week. They usually peak by the third or fourth week. The appearance of serum antibodies may be suppressed or delayed by antibiotics or corticosteroids. The current reference standard is the microscopic agglutination test (MAT), a very labor- and skill-intensive test available only in specialized reference laboratories worldwide. Paired sera drawn 14-28 days apart should be obtained. Serologic diagnosis is usually based on demonstrating a four-fold rise or single MAT titer of at least 1 in 200. To make the diagnosis of leptospirosis, it is particularly important to obtain convalescent serum, because the acute serum is often negative for antibodies. Even paired sera may fail to detect infection in up to 10% of patients with culture-positive leptospirosis. Unfortunately, serovars present in the tropics may not be represented in the serovar pool, so that sera from patients with leptospirosis from tropical areas may test negative, emphasizing the importance of obtaining cultures whenever possible.

Rapid screening serologic tests that are sometimes used include enzyme-linked immunosorbent assay (ELISA), dot-ELISA, indirect hemagglutination, IgM dipstick, latex agglutination, and indirect fluorescent antibody. These alternative tests tend to have variable sensitivities and specificities depending on the location of the test and the case definition used.

Real-time PCR offers the attractive possibility of rapid, early diagnosis. Fortunately, the test is becoming more readily available, although it is not routinely offered in most settings.

LABORATORY AND RADIOLOGIC FINDINGS

The total white blood cell count is variable but is usually elevated in severe disease. A neutrophil (polymorphonuclear) leukocytosis is common, in contrast to viral hepatitis. A mild to moderate thrombocytopenia (platelet counts 50,000-120,000/mm^3) is not uncommon and may occur in up to 50% of cases. Platelet counts of <50,000/mm^3 are less common but may be seen in severe disease. Prothrombin time may be prolonged in severe leptospirosis but can be corrected with vitamin K. Erythrocyte sedimentation rate is very commonly elevated and is often >50 mm/h.

Liver function abnormalities include elevated bilirubin (up to 20 mg/dL or higher) but with relatively mild increase in alkaline phosphatase and transaminase levels. Elevated serum amylase has been reported in 47-80% of cases, but only a few of these patients have any evidence of pancreatitis. Creatine kinase levels are elevated in over half the patients during the first week of illness. This may help to differentiate leptospirosis from viral hepatitis.

Urinalysis is abnormal in at least 70% of cases, although the abnormalities may be slight and transient, particularly in mild cases. Abnormalities may include proteinuria, hyaline or granular casts, pyuria, and hematuria.

CSF obtained during the second (immune) phase of illness shows features of an aseptic meningitis. The CSF cell count is usually <500/mm^3. Polymorphonuclear leukocytes (neutrophils) predominate early in the illness, but mononuclear cells increase later. CSF protein may be elevated (up to 300 mg/dL), but CSF glucose is usually normal.

Chest radiograph abnormalities have been noted in 23-67% of patients. Abnormalities develop 3-9 days after the onset of illness. Radiographs may be abnormal despite normal clinical examination. Abnormalities include small nodular densities, large confluent areas of consolidation, and diffuse, ill-defined, ground-glass densities. These abnormalities are usually bilateral, nonlobar, and predominantly peripheral.

TREATMENT

Antibiotic treatment should be started as soon as the diagnosis of leptospirosis is suspected, because antimicrobials are most effective if initiated during the first 4 days of illness. Early

antibiotic treatment has been shown to reduce the duration and severity of illness. There is evidence of some benefit, however, even if treatment with intravenous penicillin is started relatively late in the course of severe illness. Antibiotics should be continued for 7-10 days. The organism is sensitive to a wide range of antibiotics. Penicillin, ampicillin, amoxicillin, or doxycycline are often recommended. Erythromycin, third-generation cephalosporins such as ceftriaxone and cefotaxime, and some fluoroquinolones also appear to be very effective. The organism may be resistant to chloramphenicol, vancomycin, aminoglycosides, and first-generation cephalosporins.

In the early stages of infection, it is usually impossible to be certain of the diagnosis of leptospirosis. Hence, antibiotic coverage needs to be broad enough to include other possible diagnoses. Supportive care, if necessary in an intensive care unit, is also important, and meticulous attention to fluid and electrolyte balance is essential. Peritoneal or hemodialysis has helped to reduce mortality from leptospirosis, since in the past renal failure was an important cause of death. Jarisch-Herxheimer reactions have been reported following treatment of leptospirosis with penicillin, but they appear to be less common than with other spirochetal infections. Steroids have not yet been proved to be of any benefit.

PREVENTION

Travelers at risk of leptospirosis should be identified and counseled appropriately prior to departure. Recommendations for prevention include avoiding potentially contaminated fresh water, damp soil, or mud whenever possible; wearing protective waterproof clothing; and covering cuts and abrasions with waterproof dressings. Submersion in potentially contaminated fresh water should be avoided, since the organism can enter via the mucous membranes of the eyes, nose, and mouth. Drinking water may be contaminated with leptospires and should be purified by boiling or treating with iodine or chlorine. Filtration may not be adequate, since the organism is slender and highly motile and can pass through membrane filters up to 0.2 μm in diameter.

Travelers to areas that have recently experienced flooding may be at increased risk of infection and should be especially careful. In high-risk situations, they may be candidates for prophylactic antibiotics.

A killed whole-cell vaccine is available for immunization of high-risk humans in China, Japan, Vietnam, Israel, and certain European countries. Safety and efficacy in humans remains uncertain, however. In addition, it is important to emphasize that the vaccines are serovar-specific, and even if an inexpensive, safe, and effective vaccine were available, it would have limited value for travelers. Animal vaccines are effective and widely available but offer only short-term, serovar-specific protection. Previous infection provides protection only against the infecting serovar. Second infections are possible, therefore, in high-risk individuals with recurrent exposure to infection (e.g., rice farmers).

Chemoprophylaxis using doxycycline 200 mg once weekly, beginning prior to the first exposure and ending after the last exposure, was effective in preventing leptospirosis in US military in Panama. Short-term, high-risk travelers may be suitable candidates for chemoprophylaxis. Doxycycline 100 mg, once daily, for prevention of malaria probably also protects against leptospirosis. Travelers at risk of both malaria and leptospirosis may be particularly appropriate candidates for doxycycline chemoprophylaxis rather than alternative antimalarials such as atovaquone plus proguanil (Malarone) or mefloquine.

FURTHER READING

Adler, B., 2015. Leptospira and Leptospirosis. Springer Publishing Company, New York.

Antony, S.J., 1996. Leptospirosis—an emerging pathogen in travel medicine: a review of its clinical manifestations and management. J. Travel. Med. 3, 113–118.

CDC, 1997. Outbreak of leptospirosis among white-water rafters—Costa Rica 1996. MMWR 46, 577–579.

Faine, S., 1994. Leptospira and Leptospirosis. CRC Press, Boca Raton, FL.

Farr, R.W., 1995. Leptospirosis. Clin. Infect. Dis. 21, 1–6.

Gaynor, K., Katz, A.R., Park, S.Y., et al., 2007. Leptospirosis on Oahu: an outbreak associated with flooding of a university campus. Am. J. Trop. Med. Hyg. 76 (5), 882–886.

Griffith, M.E., Hospenthal, D.R., Murray, C.K., 2006. Antimicrobial therapy of leptospirosis. Curr. Opin. Infect. Dis. 19, 533–537.

Heron, L.G., Reiss-Levy, E.A., Jacques, T.C., et al., 1997. Leptospirosis presenting as a haemorrhagic fever in a traveler from Africa. Med. J. Aus. 167, 477–479.

Jackson, L.A., Kaufmann, A.F., Adams, W.G., et al., 1993. Outbreak of leptospirosis associated with swimming. Pediatr. Infect. Dis. J. 12, 48–54.

Katz, A.R., Ansdell, V.E., Effler, P.V., et al., 2002. Leptospirosis in Hawaii 1974–1998: epidemiologic analysis of 353 laboratory-confirmed cases. Am. J. Trop. Med. Hyg. 66 (1), 61–70.

Katz, A.R., Ansdell, V.E., Middleton, C.R., et al., 2001. Assessment of the clinical presentation and treatment of 353 cases of laboratory confirmed leptospirosis in Hawaii 1974–1998. Clin. Infec. Dis. 33 (11), 1834–1841.

Lau, C., Smythe, L., Weinstein, P., 2010. Leptospirosis: an emerging disease in travellers. Trav. Med. Inf. Dis. 8, 33–39.

Monsuez, J., Kidouche, R., LeGueno, B., et al., 1997. Leptospirosis presenting as haemorrhagic fever in a visitor to Africa. Lancet 349, 254–255.

O'Neill, K.M., Rickman, L.S., Lazarus, A.A., 1991. Pulmonary manifestations of leptospirosis. Rev. Infect. Dis. 13, 705–709.

Sasaki, D.M., Pang, L., Minette, H.P., et al., 1993. Active surveillance and risk factors for leptospirosis in Hawaii. Am. J. Trop. Med. Hyg. 48, 35–43.

Sejvar, J., Bancroft, E., Winthrop, K., et al., 2003. Leptospirosis in "Eco-challenge" athletes, Malaysian Borneo, 2000. Emerg. Infect. Dis. 9, 702–707.

Takafuji, E.T., Kirkpatrick, J.W., Miller, R.N., et al., 1984. An efficacy trial of doxycycline chemoprophylaxis against leptospirosis. N. Engl. J. Med. 310, 497–500.

Trevejo, R.T., Rigan-Perez, J.G., Ashford, D.A., et al., 1998. Epidemic leptospirosis associated with pulmonary hemorrhage—Nicaragua, 1995. J. Infect. Dis. 178, 1457–1463.

Van Crevel, R., Speelman, P., Grevekamp, C., et al., 1994. Leptospirosis in travelers. Clin. Infect. Dis. 19, 132–134.

Van de Werve, C., Perignon, A., Jaureguiberry, S., et al., 2013. Travel-related leptospirosis : a series of 15 imported cases. J. Travel Med. 20 (4), 228–231.

Watt, G., Padre, L.P., Tauzon, M.L., et al., 1988. Placebo-controlled trial of intravenous penicillin for severe and late leptospirosis. Lancet 1, 433–435.