WEIL’S SYNDROME - AN EMERGING INFECTIOUS DISEASE

*S. Swati, 1  A. Lakshmi sindhuri, 1 R.Karthikeyan2.

Department of Pharmacognosy,
1Donbosco College of Pharmacy, Pulladigunta, Guntur-522017. A.P.
2Vignan Pharmacy College, Vadlamudi, Guntur-522013.A.P.

Summary

Leptospirosis is a worldwide zoonotic infection with a much greater incidence in tropical regions and has now been identified as one of the emerging infectious diseases. The epidemiology of leptospirosis has been modified by changes in animal husbandry, climate, and human behavior. Resurgent interest in leptospirosis has resulted from large outbreaks that have received significant publicity. The development of simpler, rapid assays for diagnosis has been based largely on the recognition that early initiation of antibiotic therapy is important in acute disease but also on the need for assays which can be used more widely. In this review, the complex taxonomy of leptospires, previously based on serology and recently modified by a genotypic classification, is discussed, and the clinical and epidemiological value of molecular diagnosis and typing is also evaluated.

Key words: Leptospirosis, Assays for diagnosis, Role of Pharmacist.

*corresponding author

S.Swati,
Mobile no: 09963219073
swathisrungarapati@yahoo.co.in
Introduction

Leptospirosis, an infectious disease that affects humans and animals, is considered the most common zoonosis in the world. Leptospirosis is often referred to as swineherd's disease, swamp fever, or mud fever. The organism enters the body when mucous membranes or abraded skin come in contact with contaminated environmental sources. The infection causes a systemic illness that often leads to renal and hepatic dysfunction. Leptospirosis is caused by pathogenic spiral bacteria that belong to the genus Leptospira, the family Leptospiraceae, and the order Spirochaetales. These spirochetes are finely coiled, thin, motile, obligate, slow-growing anaerobes. Their flagella allow them to burrow into tissue. The genus Leptospira was originally thought to comprise only 2 species: L. interrogans, which is pathogenic, and L. biflexa, which is saprophytic. The prevalence is higher in males because they tend to be engaged in outdoor work more frequently than females.

History

Leptospirosis is a zoonosis of ubiquitous distribution, caused by infection with pathogenic Leptospira species. The spectrum of human disease caused by leptospires is extremely wide, ranging from subclinical infection to a severe syndrome of multiorgan infection with high mortality. This syndrome, icteric leptospirosis with renal failure, was first reported over 100 years ago by Adolf Weil in Heidelberg (5). However, an apparently identical syndrome occurring in sewer workers was described several years earlier (6, 7). Earlier descriptions of diseases that were probably leptospirosis were reviewed recently (8, 9). Leptospirosis was certainly recognized as an occupational hazard of rice harvesting in ancient China, and the Japanese name akiyami, or autumn fever, persists in modern medicine. With hindsight, clear descriptions of leptospiral jaundice can be recognized as having appeared earlier in the 19th century, some years before the description by Weil. It has been suggested that Leptospira interrogans serovar icterohaemorrhagiae was introduced to western Europe in the 18th century by westward extension of the range of Rattus norvegicus from Eurasia. The etiology of leptospirosis was demonstrated independently in 1915 in Japan and Germany. In Japan, Inada and Ido detected both spirochetes and specific antibodies in the blood of Japanese miners with infectious jaundice, and two groups of German physicians studied German soldiers afflicted by "French disease" in the trenches of northeast France. Uhlenhuth and Fromme and Hubener and Reiter (10) detected spirochetes in the blood of guinea pigs inoculated with the blood of infected soldiers. Unfortunately, these two groups became so embroiled in arguments over priority that they overlooked the first publications in English and German of papers by Inada's group, whose initial publications predated their own by 8 months. Confirmation of the occurrence of leptospirosis on both sides of the Western Front was obtained rapidly after the publication in Europe of Inada's work (11,12). Given the initial controversy over nomenclature, it is ironic that the organism had first been described almost 10 years before (13). Stimson demonstrated by silver staining the presence of clumps of spirochetes in the kidney tubules of a patient who reportedly died of yellow fever. The spirochetes had hooked ends, and Stimson named them Spirochaeta interrogans because of their resemblance to a question mark. Unfortunately, this sentinel observation was overlooked for many years. The importance of occupation as a risk factor was recognized early.
The role of the rat as a source of human infection was discovered in 1917 (14), while the potential for leptospiral disease in dogs was recognized, but clear distinction between canine infection with *L. interrogans* serovars icterohaemorrhagiae and canicola took several years. Leptospirosis in livestock was recognized some years later. Several monographs provide extensive information on the early development of knowledge on leptospirosis.

**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.

**Communability**

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.

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**Diagram Of Organism**

Scanning electron micrograph of *Scal. interrogans* serovar icterohaemorrhagiae Strain
**Biology of leptospires**

Leptospires are tightly coiled spirochetes, usually 0.1 mm by 6 to 0.1 by 20 mm, but occasional cultures may contain much longer cells. The helical amplitude is approximately 1 to 0.15 mm, and the wavelength is approximately 0.5 mm (15). The cells have pointed ends, either or both of which are usually bent into a distinctive hook (Fig. 1). Two axial filaments (periplasmic flagella) with polar insertions are located in the periplasmic space (16). The structure of the flagellar protein is complex (17). Leptospires exhibit two distinct forms of movement, translational and nontranslational (18). Morphologically all leptospires are indistinguishable, but the morphology of individual isolates varies with subculture in vitro and can be restored by passage in hamsters (19). Leptospires have atypical double membrane structure in common with other spirochetes, in which the cytoplasmic membrane and peptidoglycan cell wall are closely associated and are overlain by an outer membrane (20). Leptospiral lipopolysaccharide has a composition similar to that of other gram-negative bacteria (21), but has lower endotoxic activity (22). Leptospires may be stained using carbol fuchsin counterstain (23). Leptospires are obligate aerobes with an optimum growth temperature of 28 to 30°C. They produce both catalase and oxidase (24). They grow in simple media enriched with vitamins (vitamins B2 and B12 are growth factors), long-chain fatty acids, and ammonium salts (25). Long-chain fatty acids are utilized as the sole carbon source and are metabolized by β-oxidation.

**Types of leptospirosis**

**Anicteric Leptospirosis**

The great majority of infections caused by leptospires are either subclinical or of very mild severity, and patients will probably not seek medical attention. A smaller proportion of infections, but the overwhelming majority of the recognized cases, present with a febrile illness of sudden onset. Other symptoms include chills, headache, myalgia, abdominal pain, conjunctival suffusion, and less often a skin rash. If present, the rash is often transient, lasting less than 24 h. This anicteric syndrome usually lasts for about a week, and its resolution coincides with the appearance of antibodies. The fever may be biphasic and may recur after a remission of 3 to 4 days. The headache is often severe, resembling that occurring in dengue, with retro-orbital pain and photophobia. Myalgia affecting the lower back, thighs, and calves is often intense (26), with aseptic meningitis, whereas only 31% of patients aged 15 to 29 years did so and only 10% of those over 30 years of age. Mortality is almost nil in anicteric leptospirosis (27), but death resulting from massive pulmonary hemorrhage occurred in 2.4% of the anicteric patients (28). The differential diagnosis must include common viral infections, such as influenza, human immunodeficiency virus seroconversion (29), and, in the tropics, dengue (30, 31, 32), in addition to the bacterial causes of fever of unknown origin, such as typhoid. Turner provided a comprehensive list of other conditions that may be mimicked by leptospirosis, including encephalitis, poliomyelitis, rickettsiosis, glandular fever (infectious mononucleosis), brucellosis, malaria, viral hepatitis, and pneumonitis. Hantavirus infections must also be considered in the differential diagnosis for patients with pulmonary involvement (33). Petechial or purpuric lesions may occur, and recently, cases of leptospirosis resembling viral hemorrhagic fevers have been reported in travelers returning from Africa.
Icteric Leptospirosis

Icteric leptospirosis is a much more severe disease in which the clinical course is often very rapidly progressive. Severe cases often present late in the course of the disease, and this contributes to the high mortality rate, which ranges between 5 and 15%. Between 5 and 10% of all patients with leptospirosis have the icteric form of the disease (34). The jaundice occurring in leptospirosis is not associated with hepatocellular necrosis, and liver function returns to normal after recovery. Serum bilirubin levels may be high, and many weeks may be required for normalization (35). There are moderate rises in transaminase levels, and minor elevation of the alkaline phosphatase level usually occurs. The complications of severe leptospirosis emphasize the multisystemic nature of the disease. Leptospirosis is a common cause of acute renal failure (ARF), which occurs in 16 to 40% of cases (36). A distinction may be made between patients with prerenal azotemia (non-ARF) and those with ARF. Patients with prerenal azotaemia may respond to rehydration, and decisions regarding dialysis can be delayed for up to 72 h (37). In patients with ARF, oliguria (odds ratio [OR], 9.98) was a significant predictor of death. Serum amylase levels are often raised significantly in association with ARF (38), but clinical symptoms of pancreatitis are not a common finding (39,40,41). Necrotizing pancreatitis has been detected at autopsy (42,43). Thrombocytopenia (platelet count of <100 × 10⁹/liter) occurs in ≥50% of cases and is a significant predictor for the development of ARF (44). However, thrombocytopenia in leptospirosis is transient and does not result from disseminated intravascular coagulation (45,46). The occurrence of pulmonary symptoms in cases of leptospirosis was first noted by Silverstein (47). Subsequent reports have shown that pulmonary involvement may be the major manifestation of leptospirosis in some clusters of cases (48,49,50,51) and in some sporadic cases (52). The severity of respiratory disease is unrelated to the presence of jaundice (53). Patients may present with a spectrum of symptoms, ranging from cough, dyspnea, and hemoptysis (which may be mild or severe) to adult respiratory distress syndrome (54,55,56,57,58,59). Intra-alveolar hemorrhage was detected in the majority of patients, even in the absence of overt pulmonary symptoms (60). Pulmonary hemorrhage may be severe enough to cause death (61,62,63). The incidence of respiratory involvement varies. Rales are more common in icteric than in nonicteric leptospirosis (64). Cigarette smoking was reported as a risk factor for the development of pulmonaray symptoms (65). Radiography generally reveals diffuse small opacities which may be widely disseminated or which may coalesce into larger areas of consolidation, with increasing severity of symptoms (66,67,68). Pleural effusions may occur (69). The patchy infiltrates which are commonly seen reflect areas of intra-alveolar and interstitial hemorrhage (70). Cardiac involvement in leptospirosis is common but may be underestimated. Fatal myocarditis was first described in 1935. Clinical evidence of myocardial involvement, including abnormal T waves, was detected in 10% of 80 severe icteric cases in Louisiana, while similar electrocardiographic (ECG) abnormalities were detected in over 40% of patients in China, India, Sri Lanka, and the Philippines, including both icteric and nonicteric cases. However, in a prospective study in Malaysia, identical ECG changes were found in patients with either leptospirosis or malaria (71), and it was concluded that such ECG changes were nonspecific. Other ECG abnormalities have been reported less frequently. A mortality rate of 54% was reported in severe leptospirosis cases with myocarditis.
Transmission
Leptospirosis is spread through contact with water, soil, vegetation, or any part of a moist environment contaminated by urine or tissue of infected animals or humans. This bacteria can be inactivated by drying, but can survive in a moist environment for weeks or months. Humans and animals can become infected with urine or other body tissue. Leptospira organism can enter the body through broken skin (cut or scratch) or mucous membranes (lining of the mouth, eyes, nose, or genitalia). Infection can also occur through ingestion of contaminated water or food. If an animal is infected with a serovar or type of leptospirs that is adapted to that species of animal, then the animal will not show clinical signs of illness, but will excrete the bacteria in its urine for months or even years contaminating the environment. This serovar adaptation often occurs in rats, mice and wild life raccoon, opossums and skunks. Animals will show clinical signs of leptospirosis when infected with a serovar to which it is not adapted.

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

Pathology
The majority of infections are subclinical or extremely mild, however severe infections are possible in all target groups and natural immunity is not expected. Leptospires entering the body migrate to the lymphatic and circulatory systems within minutes, and an extremely rapid systemic infection develops thereafter - however the growth rate of leptospires is slow, therefore the incubation period can be between 2 and 28 days - typically ranging between 3 and 14 days. In all cases the onset of symptoms is very sudden, with a severe and incapacitating headache seen in over 90% of cases. Bilateral conjunctival suffusion, signs of meningism and pyrexia of 39°C or above are expected. A red transient pinprick non-blanching rash is often seen, and patients frequently complain of myalgia, fatigue and nausea. There may be a nonproductive cough but with minor haemoptysis. Psychological changes are often seen, with patients feeling depressed, confused, aggressive and sometimes psychotic - with schizophrenia and hallucinations, personality changes and violence. The bacteria are present in the bloodstream during the first few days (S0 to S9) and so can be directly isolated. After this period the bacteria are confined to the tissues and testing must rely on detection of antibodies.

Uniphase infections
In mild cases the infection follows a single phase, lasting 3 to 7 days, with the above symptoms appearing on day S0, peaking on day S2 and reducing thereafter. It can often therefore be misdiagnosed as one of the multitude of other pyrexic infections. Antibiotics can still be of benefit but patients will recover without intervention.

Biphasic infection
In moderate and severe cases the infection follows two phases, the initial septicaemic phase as above, followed by a transient remission, then a rapid decline one or two days later. Icteric symptoms present during this second phase, and without intervention it usually progresses to
mortality within a short time. Biphasic pathology does not always indicate a severe infection, and indeed in the most virulent cases the distinction is lost, with the patient rapidly deteriorating from SO and without treatment often dying within ten days.

**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 tissue 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 immunohistochemical 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 (73, 74, 75, 76, 77).
Preventive measures

Environmental Measures

- To prevent illness, prevent contamination of living, working, and recreational areas by urine of infected animals.
- Control rodent populations in areas of human habitation.
- Domestic animal owners should take necessary precautions to minimize their animal’s potential contact with wildlife (e.g., do not feed pets outside or allow animals to roam unsupervised).
- Do not allow animals to urinate in or near ponds, pools, or puddles.
- Keep animals away from gardens, playgrounds, sandboxes, and other places children may play.
- Among domesticated animals, vaccination of swine, cattle, and dogs does not provide 100% protection. Vaccines are generally effective in preventing symptoms of disease in animals, but do not protect against all serotypes and do not protect completely against infection or prevent shedding of organisms in the urine (78, 79).

Role of pharmacist in prevention of Weil’s syndrome

- The pharmacists have to advice and educate the public to prevent leptospirosis, on how the disease is transmitted and the importance of proper food storage and garbage disposal.
- They should also be counseled to minimize their contact with fresh water, mud, and vegetation that might be contaminated with the urine of infected animals.
- If their occupation or recreational activities require such exposure, education on use of personal protective measures (i.e., proper clothing, footwear, and gloves) should be given. Additional preventive measures include:
  - Always wash hands thoroughly after touching items potentially soiled by an animal’s urine.
  - Use a disinfectant cleaning solution or a solution of one part bleach in ten parts water to clean areas or items soiled by the animal’s urine.
Treatment

Treatment of leptospirosis differs depending on the severity and duration of symptoms at the time of presentation. Patients with mild, flu-like symptoms require only symptomatic treatment but should cautioned to seek further medical help if they develop jaundice. Patients who present with more severe anicteric leptospirosis will require hospital admission and close observation. If the headache is particularly severe, a lumbar puncture usually produces a dramatic improvement.

The management of icteric leptospirosis requires admission of the patient to the intensive care unit initially. Patients with prerenal azotemia can be rehydrated initially while their renal function is observed, but patients in acute renal failure require dialysis as a matter of urgency. This is accomplished satisfactorily by peritoneal dialysis (80,81,82). Cardiac monitoring is also desirable during the first few days after admission (83).

Specific antibiotic treatment was reported soon after penicillin became available, with mixed results (84). Oxytetracycline was also used (85). Early experience was summarized by Alston and Broom in their monograph (86). Few well-designed and well-controlled studies of antibiotic treatment have been reported (87). A major difficulty in assessing the efficacy of antibiotic treatment results from the late presentation of many patients with severe disease, after the leptospires have localized in the tissues.

Doxycycline (100 mg twice a day for 7 days) was shown to reduce the duration and severity of illness in anicteric leptospirosis by an average of 2 days (88). Patients with severe disease were excluded from this study. Two randomized studies of penicillin produced conflicting results. One study included 42 patients with severe leptospirosis, of whom 19 were jaundiced (89); no patient required dialysis and there were no deaths. Intravenous penicillin was given at a dosage of 6 MU/day for 7 days and found to halve the duration of fever. A second study included 79 patients with icteric leptospirosis, of whom 4 died (90). Patients in the treatment group received intravenous penicillin at a dose of 8 MU/day for 5 days. No difference was observed between treatment and control groups in outcome or duration of the illness. There have been no controlled trials of penicillin versus doxycycline for treatment of leptospirosis.

A consistent finding of these studies has been the prevention of leptospiruria or a significant reduction in its duration. This finding alone is sufficient justification for antibiotic use, but any antibiotic treatment should be started as early as possible and should not replace other therapeutic measures. Jarisch-Herxheimer reactions have been reported after penicillin administration (91,92). However, the apparently low risk should not preclude the use of penicillin.

Doxycycline (200 mg orally, once weekly) has been shown to be effective for short-term prophylaxis in high-risk environments (93). Similar findings have been reported in rhesus monkeys challenged experimentally (94). In a recent controlled trial, doxycycline significantly reduced the incidence of clinical disease but not serological evidence of infection. Anecdotal evidence suggests that doxycycline but not penicillin may be used successfully after exposure in laboratory accidents (95). An evidence-based review of antibiotic prophylaxis has been published.
Conclusion

The history and lethal effects of leptospirosis have been understood for many years, and this knowledge has led to the development of effective preventive strategies. In developed countries, leptospirosis continues to be a disease of considerable economic significance in animal husbandry, but the major burden of human disease remains in tropical and subtropical developing countries. The development of several promising approaches to rapid diagnosis has been based largely on the recognition that early initiation of antibiotic therapy is important in acute disease, but also on the need for simpler assays which can be used more widely. However, many of these diagnostic advances will be unavailable to those populations for which they would be most useful. At a more fundamental level, understanding of the mechanisms of pathogenesis remains incomplete, but recent advances in the molecular biology of leptospires offer the prospect of more rapid progress in the future.

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