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LEPTOSPIROSIS IN INDIA: A VETERINARY PERSPECTIVE

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Abstract: Leptospirosis is an acute anthropo-zoonotic infection of worldwide significance caused by spirochaete *Leptospira interrogans* which has 23 serogroups and >200 serovars. Various factors influencing the animal activity, suitability of the environment for the survival of the organism and behavioral and occupational habits of human beings can be the determinants of incidence and prevalence of the disease. The disease was considered inconsequential till recently, but it is emerging as an important public health problem during the last decade or so due to sudden upsurge in the number of reported cases and outbreaks. It is a zoonotic disease that is spread primarily by rodents. It has become an important cause of acute febrile illness in children in India during the monsoon and immediate post-monsoon periods. In recent times, it has also become common to encounter cases of leptospirosis throughout the year in urban areas due to poor sanitation, water logging, overcrowding, and mushrooming of slums.

Keywords: Leptospirosis, Weil's Disease, Canicola Fever, Occupation Hazzards,Epidemiolog.

1. Historical Review

In 1886 Adolf Weil first described this disease among agricultural workers in Germany. Fieldler, later in 1888 named this disease as “Weil's disease”. In 1915 Inado and Ido demonstrated the causative agent in Japan and by Huebner and Reiter, in Germany. Noguchi in 1917 isolated leptospires in his own medium and suggested a generic name “*Leptospira*”. In 1886 Ido and his associate's isolated leptospires from kidneys of rats and subsequently very many workers isolated different leptospires and identified them under different serogroups. The first isolate made during 1917 from a patient in Japan with jaundice and hemorrhagic manifestations was named as “icterohaemorrhagiae”. Later they could also isolate serovar “hebdomadis” from a patient with seven days fever (nonicteric) in 1918 and serovar “autumnalis” from autumnal fever patient in 1925. In Indonesia serovar “bataviae” was isolated (1925) from anicteric patient. The first animal isolate was serovar “grippotyphosa” in cattle from USSR in 1928. Later “canicola” from Netherlands (1933), “australis” and “Pomona” from Ballice (1937), “saxkoebing” and “ballum” from Denmark (1944) and other

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members of different serogroups were subsequently isolated in various places of the world from different animal and reservoir hosts.

2. Etiology

Order: Spirochaetales

Family: Leptospiraceae

Genus: Leptospira

The genus at present consists of two species: “L. interrogans” and “L. biflexa”. The former species is pathogenic to man and animals while the latter is saprophytic and can be found in fresh water, tap water and salt water.

3. Transmission

Leptospires may be transmitted to humans through the following routes:

- Direct contact with infected urine or animals (especially occupational). The usual portal of entry is through abrasions or cuts in the skin or via the conjunctiva.
- Indirectly via contaminated soil or water, especially in times of flood. Infection may take place via intact skin after prolonged immersion in water, but this usually occurs when abrasions are likely to occur and is thus difficult to substantiate.
- Ingestion of infected water. Water-borne transmission has been documented; point contamination of water supplies has resulted in several outbreaks of leptospirosis.
- Inhalation of water or aerosols also may result in infection via the mucous membranes of the respiratory tract.

4. Hosts Involved

Maintenance hosts: rats, pigs, cattle, bandicoots, dogs and cats.

Accidental (incidental) hosts: Humans and other animals.

The disease is maintained in nature by chronic infection of the renal tubules of maintenance hosts. A maintenance host is defined as a species in which infection is endemic and is usually transferred from animal to animal by direct contact. Infection is usually acquired at an early age, and the prevalence of chronic excretion in the urine increases with the age of the animal. Other animals (such as humans) may become infected by indirect contact with the maintenance host. Animals may be maintenance hosts of some serovars but incidental hosts of others, infection with which may cause severe or fatal disease. The most important maintenance hosts are small mammals, which may transfer infection to domestic farm animals, dogs, and humans. The extent to which infection is transmitted depends on many factors, including climate, population density, and the degree of contact between maintenance and accidental hosts.

Domestic animals are also maintenance hosts; dairy cattle may harbor serovars *hardjo, pomona,* and *grippotyphosa*; pigs may harbor *pomona, tarassovi or bratislava*; sheep may harbour *hardjo* and *pomona*; and dogs may harbour canicola. Distinct variations in maintenance hosts and the serovars they carry occur throughout the world. Human infections may be acquired through occupational, recreational, or vocational exposures. Occupation is a significant risk factor for humans. Direct contact with infected animals accounts for most infections in farmers, veterinarians, abattoir workers, meat inspectors, rodent control workers, and other occupations which require contact with animals. Indirect contact is important for sewer workers, miners, soldiers, septic tank cleaners, fish farmers, gamekeepers, canal workers, rice field workers, taro farmers, banana farmers, and sugar cane cutters.

There is a significant risk associated with recreational exposures occurring in water sports, including swimming, canoeing, white water rafting, fresh water fishing, and other sports where exposure is common, such as potholing and caving. The potential for exposure of large numbers of individuals occurs during competitive events. Several outbreaks of leptospirosis associated with water have been reported. Many of these outbreaks have followed extended periods of hot, dry weather, when pathogenic leptospires presumably have multiplied in freshwater ponds or rivers. Cases of leptospirosis also follow extensive flooding.

5. Epidemiology

Leptospirosis is presumed to be the most widespread zoonoses in the world. The incidence is significantly higher in warm-climate countries than in temperate regions; this is due mainly to longer survival of leptospires in the environment in warm, humid conditions. However, most tropical countries are also developing countries, and there are greater opportunities for exposure of the human population to infected animals, whether livestock, domestic pets, or wild or feral animals. The disease is seasonal, with peak incidence occurring in summer or fall in temperate regions, where temperature is the limiting factor in survival of leptospires, and during rainy seasons in warm-climate regions, where rapid desiccation would otherwise prevent survival.

Three epidemiological patterns of leptospirosis were defined by Faine.

- The first occurs in temperate climates where few serovars are involved and human infection almost invariably occurs by direct contact with infected animals though farming of cattle and pigs. Control by immunization of animals and/or humans are potentially possible.
- The second occurs in tropical wet areas, within which there are many, more serovars

infecting humans and animals and larger numbers of reservoir species, including rodents, farm animals, and dogs. Human exposure is not limited by occupation but results more often from the widespread environmental contamination, particularly during the rainy season. Control of rodent populations, drainage of wet areas, and occupational hygiene are all necessary for prevention of human leptospirosis. These are also the areas where large outbreaks of leptospirosis are most likely to occur following floods, hurricanes, or other disasters.

- The third pattern comprises rodent-borne infection in the urban environment. While this is of lesser significance throughout most of the world, it is potentially more important when the urban infrastructure is disrupted by war or by natural disasters. This type of infection is now rarely seen in developed countries, but is exemplified by the recent rediscovery of urban leptospirosis in Baltimore and by outbreaks occurring in slum areas in developing countries.

Seroepidemiologic and clinical studies show that the disease is endemic in Andaman Islands and southern states of India (Loganathan N et al., 2012). The seroprevalence is reported to be high (52.7%) among high-risk population in Andaman Islands and 19.8% and 9.3% in Madras and Bangalore respectively. (Seal SC et al., 1969). In India, the disease has been found more commonly associated with natural disasters especially during the monsoon period at which times acute epidemics may eventuate. A multi-centric study in India showed that leptospirosis accounts for about 12.7% of cases of acute febrile illness responsible for attendance at hospitals. Carrier animals include rats, pigs, cattle, bandicoots and dogs. The predominant serovars are *copenhageni, autumnalis, pyrogenes, grippotyphosa, canicola, australis, javanica, sejroe, louisiana, and pomona*. The disease is endemic in Kerala Tamilnadu, Gujarat, Andamans, Karnataka, and Maharashtra. It has also been reported from Andhra Pradesh, Orissa, West Bengal, Uttar Pradesh, and Delhi & Puducherry. Rodents, domestic & wild animals form the reservoir of infection where domestic animals such as cattle, dogs, and pigs may act as carriers for several months (temporary carrier) while rodents usually remain carrier throughout their life (permanent carrier). Leptospires are excreted in the urine of the animals and they affect man when he comes into contact with urine of infected animals, directly or indirectly, when he is exposed to an environment contaminated by the urine of the infected animals such as soil and surface water following monsoon rains. Leptospirosis can manifest in many ways.

6. Clinical Features of Leptospirosis

According to information provided by the World Health Organization, the disease can present in one of four ways:

i. As a mild influenza-like illness

ii. As Weil's syndrome, characterized by jaundice, renal failure, hemorrhage, and myocarditis with arrhythmias

iii. As meningitis/meningoencephalitis

iv. As pulmonary hemorrhage with respiratory failure

Most patients have subclinical or very mild illness. The exact ratio of asymptomatic to symptomatic leptospirosis in children (from India) is not available as most of the infections are either subclinical or have nonspecific manifestations, indistinguishable from that of other common febrile illnesses. In a study from the Andaman and Nicobar islands (India), 90% of school children had subclinical or unnoticed infections. It was also seen that children who had had the infection earlier (i.e., were previously seropositive) suffered less morbidity and mortality in subsequent outbreaks. The clinical presentation of leptospirosis varies widely; it can range from an acute febrile illness to a severe syndrome of multiorgan dysfunction and therefore the diagnosis may be missed unless the physician has a high index of suspicion for the disease. Symptomatic infection presents as a sudden-onset febrile illness with nonspecific signs and symptoms (70%) or as aseptic meningitis (20%) or hepatorenal dysfunction (10%). Both anicteric (90% or more cases) and icteric leptospirosis are known to occur. The more common, mild, anicteric form of the disease is characterized by nonspecific symptoms such as fever, headache, chills, myalgia, nausea, and abdominal pain, while the severe, potentially fatal, icteric form of leptospirosis (Weil's syndrome) is characterized by renal, hepatic, and vascular complications.

7. Diagnosis

7.1. General Clinical Laboratory Findings

In anicteric disease, the erythrocyte sedimentation rate is elevated, and white cell counts range from below normal to moderately elevated. Liver function tests show a slight elevation in aminotransferases, bilirubin, and alkaline phosphatase in the absence of jaundice. Urinalysis shows proteinuria, pyuria, and often microscopic hematuria. Hyaline and granular casts may also be present during the first week of illness. Lumbar puncture will usually reveal a normal or slightly elevated CSF pressure and may serve to reduce the intensity of headache. CSF examination may initially show a predominance of polymorphs or lymphocytes, but later examination almost invariably shows that lymphocytes predominate. CSF protein may be normal or elevated, while CSF glucose is usually normal. In patients with severe jaundice, xanthochromia may occur. CSF abnormalities are common in the second week of illness, and

CSF pleocytosis can persist for weeks.

In severe leptospirosis, a peripheral leukocytosis occurs with a shift to the left, whereas in dengue, atypical lymphocytes are commonly observed. Thrombocytopenia is common and may be marked. Renal function impairment is indicated by raised plasma creatinine levels. The degree of azotemia varies with severity of illness. In icteric leptospirosis, liver function tests generally show a significant rise in bilirubin, with lesser increases in transaminases and marginal increases in alkaline phosphatase levels. The increase in bilirubin is generally out of proportion to the other liver function test values. Similar findings were reported for serum creatinine phophokinase levels. Serum amylase may also be elevated, particularly in patients with ARF.

7.2. Microscopic Demonstration

Leptospires may be visualized in clinical material by dark-field microscopy or by immunofluorescence or light microscopy after appropriate staining. Dark-field microscopic examination of body fluids such as blood, urine, CSF, and dialysate fluid has been used but is both insensitive and lacking specificity. Approximately 10^4 leptospires/ml are necessary for one cell per field to be visible by dark-field microscopy. A quantitative Buffy coat method was recently shown to have a sensitivity of approximately 10^3 leptospires/ml. A method which involved repeated microscopic examination of double-centrifuged anticoagulated blood demonstrated leptospires in 32% of patients whose leptospirosis was confirmed by animal inoculation. Microscopy of blood is of value only during the first few days of the acute illness, while leptospiremia occurs. In volunteers infected with serovar *grippotyphosa*, leptospires were detected as early as 4 days prior to the development of symptoms. Most authorities agree that there are too few leptospires in CSF for detection by dark-field microscopy. Direct dark-field microscopy of blood is also subject to misinterpretation of fibrin or protein threads, which may show Brownian motion.

7.3. Staining Methods

These methods have been applied to increase the sensitivity of direct microscopic examination. These have included immunofluorescence staining of bovine urine, water, and soil and immunoperoxidase staining of blood and urine. A variety of histopathological stains have been applied to the detection of leptospires in tissues. Leptospires were first visualized by silver staining, and the Warthin-Starry stain is widely used for histological examination. Immunofluorescence microscopy is used extensively to demonstrate leptospires in veterinary specimens. More recently, immunohistochemical methods have been applied.

7.4. Antigen Detection

Detection of leptospiral antigens in clinical material would offer greater specificity than dark-field microscopy while having the potential for greater sensitivity. An evaluation of several methods concluded that radioimmunoassay (RIA) could detect 10^4 to 10^5 leptospires/ml and an enzyme-linked immunosorbent assay (ELISA) method could detect 10^5 leptospires/ml, but countercurrent immunoelectrophoresis and staphylococcal coagglutination were much less sensitive. RIA was more sensitive than dark-field microscopy but less sensitive than culture when applied to porcine urine. A double-sandwich ELISA could detect 10^4 leptospires of serovar *hardjo* but was less sensitive for other serovars. A chemiluminescent immunoassay was applied to human blood and urine but was no more sensitive than earlier ELISA. More recently, immunomagnetic antigen capture was combined with fluoroimmunoassay to detect as few as 10^2 leptospires/ml in urine of cattle infected with serovar *hardjo*. Inhibitory substances have been reported in urine, indicating the need for treatment of urine prior to testing.

7.5. Isolation of Leptospires

Leptospiremia occurs during the first stage of the disease, beginning before the onset of symptoms, and has usually finished by the end of the first week of the acute illness. Therefore, blood cultures should be taken as soon as possible after the patient's presentation. One or two drops of blood are inoculated into 10 ml of semisolid medium containing **5-**fluorouracil at the patient's bedside. For the greatest recovery rate, multiple cultures should be performed, but this is rarely possible. Inoculation of media with dilutions of blood samples may increase recovery. Rapid detection of leptospires by radiometric methods has been described. Leptospires survive in conventional blood culture media for a number of days. Rarely, leptospires have been isolated from blood weeks after the onset of symptoms.

Other samples that may be cultured during the first week of illness include CSF and dialysate. Urine can be cultured from the beginning of the second week of symptomatic illness. The duration of urinary excretion varies but may last for several weeks. Survival of leptospires in voided human urine is limited, so urine should be processed immediately by centrifugation, followed by resuspending the sediment in phosphate-buffered saline (to neutralize the pH) and inoculating into semisolid medium containing 5-fluorouracil. Cultures are incubated at 28 to 30°C and examined weekly by dark-field microscopy for up to 13 weeks before being discarded. Contaminated cultures may be passed through a 0.2-μm or 0.45-μm filter before subculture into fresh medium.

Table 1. Some media used for the isolation of Leptospira isolation.

Nature of the media	Serum enriched	Serum replaced by albumin ans tween	Chemically defined medium
Liquid	Korthof's	EMJH, PLM-5,	Shenberg's Vogel and Hunter
Liquid	Stuart's	Leptospira 5x	
Liquid	Vervoot's	Protein free media	
Semisolid	Fletcher's	Semisolid EMJH	
Semisolid	Noguchi's		
Solid	Cox's		
Solid	Korthof's		

7.6. Identification of Leptospiral isolates

Isolated leptospires are identified either by serological methods or, more recently, by molecular techniques. Traditional methods relied on cross-agglutinin absorption. The number of laboratories which can perform these identification methods is very small. The use of panels of monoclonal antibodies allows laboratories which can perform the microscopic agglutination test to identify isolates with relative rapidity. Molecular methods have become more widely used and are discussed below.

7.7. Other Serological tests

Because of the complexity of the MAT, rapid screening tests for leptospiral antibodies in acute infection have been developed. Complement fixation (CF) was widely used, but methods were not standardized. CF was applied to veterinary diagnosis, but species-specific differences were noted. CF tests have generally been replaced by ELISA methods. IgM antibodies become detectable during the first week of illness, allowing the diagnosis to be confirmed and treatment initiated while it is likely to be most effective. IgM detection has repeatedly been shown to be more sensitive than MAT when the first specimen is taken early in the acute phase of the illness. IgM antibodies have been detected by ELISA in CSF from patients with icteric leptospirosis. In patients with meningitis without a proven etiology, IgM was detected in the CSF in 15%. IgM has been detected in saliva, and a dot-ELISA using polyester fiber was developed to facilitate collection of saliva directly onto the support material.

ELISA methods have been applied in a number of modifications. An IgM-specific dot-ELISA was developed in which polyvalent leptospiral antigen was dotted onto nitrocellulose filter disks in microtitre tray wells, allowing the use of smaller volumes of reagents. Further modifications of this approach have been used to detect IgG and IgA in addition to IgM and have employed an immunodominant antigen and a polyester fabric-resin support in place of nitrocellulose. A commercial IgM dot-ELISA dipstick has been shown to be

as sensitive as a microtiter plate IgM-ELISA. Another dipstick assay has been extensively evaluated in several populations. A dot immunoblot assay using colloidal gold conjugate allowed completion of the assay within 30 min.

7.8. Molecular Diagnosis

Leptospiral DNA has been detected in clinical material by dot-blotting and in situ hybridization. A recombinant probe specific for pathogenic serovars was prepared from serovar *lai*. Probes specific for serovar *hardjo*bovis were developed and applied to the detection of leptospires in bovine urine. However, the sensitivity of ^{32}P-labeled probes was approximately 10^3 leptospires, much lower than the sensitivity of PCR, and probes have not been used extensively for diagnosis since PCR became available.

8. 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 be cautioned to seek further medical help if they develop jaundice. Specific antibiotic treatment was reported soon after penicillin became available, with mixed results. Oxytetracycline was also used. Few well-designed and well-controlled studies of antibiotic treatment have been reported. 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. Parenteral penicillin G (6-8 million U/m ^{2} /day given intravenously in divided doses every 4 hours for 7 days) is the drug of choice. Tetracycline (10-20 mg/kg/day given orally or intravenously in divided doses every 6 hours for 7 days) can be used in those allergic to penicillin. Doxycycline has been successfully used in adults. Oral amoxicillin (25-50 mg/kg/day in two or three divided doses) is an alternative therapy for children < 9 years of age. Although ciprofloxacin has been occasionally used for treatment (especially in patients with uveitis), there is a need for more trials to evaluate its efficacy in both adults and children.

9. Prevention and Control

Leptospirosis is a preventable disease.

- Important measures for prevention are rodent control and avoidance of contact with contaminated water and soil.
- Parents should instruct children not to wade through flood waters or play in puddles/stagnant water.

- Vaccination:
- On-going research into numerous vaccine preparations for humans and animals is well documented. This includes the use of inactivated and attenuated vaccines, recombinant protein or lipoprotein vaccines, LPS vaccines and DNA vaccines.
- Immunization of livestock (cattle, sheep, pigs, and horses) and family pets (cats and dogs) has been recommended as a means of eliminating some of the animal reservoirs.
- Social control measures:
- Effective risk communication strategies such as awareness, health promotion and health education, advocacy and capacity building. Leptospirosis has typically been considered an occupational disease and thus social control measures directed towards agriculture and other at-risk workers are critical.
- Improvement in sanitation and living conditions, and rodent control
- The use of rodenticides, entrapment of animals, and improved sanitation have been shown to successfully diminish the risk of leptospirosis transmission. In India, the timing of rodent control was shown to be a vital consideration in the prevention of disease transmission. The rodent breeding period starts with the southwest monsoon, suggesting that rodent control measures in the pre-monsoon period would bring better vector control.
- Prophylactic and therapeutic medical and veterinary interventions:
- Doxycycline (200 mg orally once a week) is used as prophylaxis in adults traveling to a highly endemic area for a limited period of time and also during outbreaks, but its use in children has not been studied.
- Surveillance systems:
- A functional disease surveillance system, for both humans and animals, is essential for the effective control of leptospirosis. In addition to a number of research institutions, there are three WHO collaborating centers for leptospirosis in the region: the WHO/FAO/OIE Collaborating Centre for Reference and Research on Leptospirosis, Australia and Western Pacific Region based in Brisbane, Australia, and the Regional Medical Research Center in Port Blair, India.

10. Conclusion

Leptospirosis is characterised by the renal and hepatic involvement; extensive pulmonary disease is not commonly discussed. [1, 3] In the present study, liver and kidney though the commonest organs involved, were not responsible for mortality. On the other hand, there was high incidence of pulmonary haemorrhage and the resultant high mortality. Respiratory

manifestations have been reported sporadically in the literature. [4-9] Mortality due to leptospirosis is two fold higher in cases with pulmonary involvement. [5] Dupont et al have implicated dyspnoea and alveolar infiltration as independent poor prognostic factors, associated with high mortality. [7] Alveolar haemorrhage has been reported even before the onset of renal or hepatic involvement. [8] The pathogenesis of alveolar haemorrhage in leptospirosis is not well understood. The occurrence of alveolar haemorrhage in the absence of coagulopathy or thrombocyto-paenia in many cases is presumably due to capillary fragility which is characteristic of the disease. [9] The basic pathology in leptospirosis is vasculitis. [1] The commonest cause of alveolar haemorrhage, in patients without leptospirosis is vasculitis. Thus, it should be considered to be the most important factor for the pathogenesis of alveolar haemorrhage in leptospirosis too. The most important diagnostic test for immune mediated alveolar haemorrhage is antineutrophil cytoplasmic antibody (ANCA). Studies on the role of ANCA in leptospiral alveolar haemorrhage have not been carried out so far. In view of the high mortality associated with the condition, other treatment modalities like immunosuppression and plasmapheresis should be explored, as attempted by Borer et al [11].

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