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Research Paper

LEPTOSPIROSIS IN HUMANS: AN OVERVIEW

Sujata S Bhave[1*]

*Corresponding Author: Sujata S Bhave, ✉ sujata0bhave@gmail.com

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Leptospirosis is a zoonotic infection that has a global distribution. The disease is caused by the Leptospira, a spirochete. Human leptospirosis is caused due to exposure to contaminated fresh water. Majority of the infections are asymptomatic but when symptoms develop they range from a mild, self-limiting, non-specific febrile illness to fulminant respiratory and renal failure with high case fatality rate. The most characteristic form of the disease is termed as Weil's disease which is associated with jaundice, renal failure and hemorrhage. Diagnosis of leptospirosis is most commonly done by serological methods and microscopic agglutination test is called as the "gold standard". Oral doxycycline is the drug of choice for mild cases. In this review etiology, transmission, clinical presentation, diagnosis, treatment and prevention aspects of leptospirosis are discussed in detail.

Keywords: Leptospirosis, Humans, Infectious disease

INTRODUCTION

Leptospirosis, a zoonotic disease with global distribution, is caused by the spirochetal bacteria *Leptospira*. Clinical manifestations are often non-specific and can range from being asymptomatic to life threatening multi-system organ failure. Nearly 1.03 million cases with 58900 associated deaths due to leptospirosis have recently been documented (Costa *et al*., 2015). The incidence of disease is underreported because of reasons such as mild and nonspecific nature of disease and challenging nature of definitive laboratory diagnosis. Moreover, leptospirosis is not included in the list of reportable diseases including countries such as United States as well as various other developing countries with high endemicity (Bharti *et al*., 2003; and Pappas *et al*., 2008). The incidence of leptospirosis in tropical regions is ten times higher than other regions of the world owing to environmental factors such as humidity, higher temperatures and rainfall which aids survival of organisms as well as socioeconomic factors such as poor sanitation facilities, closer contact of humans with rodents and domestic animals (Hartskeerl *et al*., 2011; and Leshem *et al*., 2011). Leptospirosis is considered as an occupational disease in which farmers/ranchers, veterinarians, farmers, military

[1] Senior Research Fellow, Department of Veterinary Public Health, Bombay Veterinary College, Parel, Mumbai 400012, India.

personnel, ecologists who likely get more exposure to animals or water are at higher risk of acquiring leptospirosis (Katz *et al*., 2001). Infections associated with travel and recreational exposures are the leading sources of acquiring leptospirosis infection in developed countries. Several cases of infection have been linked to water bases activities viz. swimming, triathlons, kayaking and canoeing, including many outbreaks in the United States and other developed countries (Katz *et al*., 2001; and Nardone *et al*., 2004).

ETIOLOGY

Bacterial spirochetes of the genus *Leptospira* are the cause of leptospirosis. The 21 identified *Leptospira* species are classified according to genetic relatedness and 9 out of them are considered to be pathogenic (Haake and Levett, 2015a). The organisms are also categorized as per serogroup. Currently, more than 26 pathogenic serogroups and 250 pathogenic serovars have been identified with over 60 nonpathogenic serovars (Schreier *et al*., 2013; and Haake and Levett, 2015a). The leptospires are thin, motile and corkscrew-shaped organisms with a end hook which is a characteristic of organism. The spirochetes are anaerobic organisms which can be best grown between 28-30 °C and therefore can persist in the environments such as water and soil for months where they are widely spread (Schreier *et al*., 2013; and Haake and Levett, 2015b). In addition, animals act as natural reservoirs for *Leptospira* species, as they are commensals of renal tubules of many species of animals – majorly rodents but also other animals including livestock (Schreier *et al*., 2013). The constant environmental presence of the organisms is attributed to the shedding from kidneys and excretion in urine from the colonized animals.

TRANSMISSION

The most common route of transmission of infection to humans is via contact with damp soil or water contaminated with leptospires but transmission can also happen through direct contact with blood or urine from the colonized or infected animal (Haake and Levett, 2015a). The typical route of entry of organism to human body is through mucous membrane (oral mucosa, conjunctivae) or cuts and abrasions but the organisms are unable to penetrate intact skin (Haake and Levett, 2015b). Water contaminated with pathogenic *Leptospira* can rarely lead to infection by the feco-oral route with accidental ingestion of organisms (Haake and Levett, 2015a and 2015b). Infection can be caused via respiratory route with inhalation of aerosolized organisms (Haake and Levett, 2015a and 2015b). After entering into the body, *Leptospira* multiply into the bloodstream and spread throughout the body vie hematogenous route. Organisms have ability to affect to each and every organ system of the body because of its potential to cross tissue barriers without any difficulty before the host antibody response dismisses them from the blood (Haake and Levett, 2015a and 2015b).

CLINICAL PRESENTATION

Clinical features of leptospirosis vary in severity from a mild, self-limited febrile illness to a fulminant life-threatening illness. The average incubation period ranges from 7 to 12 days however it can be as short as 3 days or can be as long as a month (Haake and Levett, 2015b). A biphasic pattern of disease is seen in 90% of symptomatic cases in which an initial

symptomatic leptospiremic phase lasts from 5 to 7 days that is followed by an immune phase wherein symptoms steadily improve because antibody response is initiated by the host. However, the two phases may be difficult to differentiate clinically (Haake and Levett, 2015a). Typically the onset of infection occurs with abrupt fever, chills mylgias and headache which is comparable to many other febrile illness (Haake and Levett, 2015a). Muscle pain caused in leptospirosis is typically seen in the calves and lower back, and frontal and throbbing headache is characteristic of leptospirosis (Haake and Levett, 2015b). The most pathognomonic physical finding of the infection is the conjunctival suffusion i.e. dilatation of conjunctival vessels without purulent exudate. (Haake and Levett, 2015b). Gastrointestinal symptoms such as anorexia, nausea, vomiting and diarrhea are common and around half of the patients present nonproductive cough (Haake and Levett, 2015b). Aseptic meningitis is observed in approximately 80% of cases which begin from around 7th day of illness (Haake and Levett, 2015a). Hepatosplenomegaly, lymphadenopathy, or pharyngitis are less frequently observed in leptospirosis.

Leptospirosis can advance into severe, fulminant disease in a minority of cases with mortality ranging from 5% to 40% (Haake and Levett, 2015a). The combination of manifestations such as jaundice, renal failure and hemorrhage is termed as Weil's disease and is the most distinguishing from associated with associated with sever leptospirosis. In this form, because of extensive hematogenous dissemination of bacteria during *Leptospira*emic phase, any organ system in the body can be affected. Renal tubules are the predilection sites for the organisms in their natural hosts and thus kidney involvement is common in leptospirosis with renal failure occurring in 16% to 40% of cases (Abdulkader, 1997). Renal dysfunction caused due to leptospirosis is generally non-oliguric and it is associated with hypokalemia. Appropriate supportive care can recover the renal function, however higher mortality is liked to its presence (Taylor *et al*., 2015). Liver is typically affected in a cholestatic pattern with increase in conjugated bilirubin levels and slight elevations in serum aminotransferase (Lane and Dore, 2016). Liver failure is commonly reversible though slow and cannot independently contribute in increasing mortality (Haake and Levett, 2015b). Severe form of leptospirosis lead to pulmonary manifestations including alveolar hemorrhage which is also termed as severe pulmonary hemorrhagic syndrome or SPHS and pulmonary edema, both of which can result in Acute Respiratory Distress Syndrome (ARDS) (Helmerhorst *et al*., 2012). Considerably higher mortality is associated with pulmonary involvement with case fatality rates ranging from 50% to 70% (Segura *et al*., 2005; and Costa *et al*., 2015). Heart involvement can also be seen in leptospirosis and nonspecific echocardiogram abnormalities are observed even in mild infection. Pericarditis, myocarditis, arrhythmias and heart block may occur but, replorization abnormalities are the signs of poor prognosis (Haake and Levett, 2015a). After recovery, patients may continue to have sequelae in form of neuropsychiatric and ocular symptoms (WHO, 2003).

DIAGNOSTIC TESTING

The non-specific clinical symptoms and significant similarity with various other febrile illnesses with exposure history as well as symptoms prompt the need of confirmatory

diagnosis. Commonly, confirmatory diagnosis of leptospirosis infection can be done either by traditional microbiological methods such as direct detection and culture or serology. Spirochetes including *Leptospira* poorly stains with traditional staining methods and is best observed under dark field microscopy, however sensitivity and specificity of these methods are poor while testing clinical samples (Vijayachari *et al*., 2001; and Schreier *et al*., 2013). *Leptospira* from clinical samples of patients generally take 1-2 weeks to grow but can even take a month in laboratory conditions and special growth media is essential. During the initial 10 days of illness, diagnosis with blood and CSF cultures is most useful because during that period organisms are spreading hematogenously in the body (WHO, 2003; and Schreier *et al*., 2013). Urine cultures for *Leptospira* are more likely to be positive after the second week of illness due to affinity of the organisms with renal tubules. The samples can show positive results for up to 30 day after dismissal of symptoms.

Serological methods are the most common tools used to confirm the diagnosis of leptospirosis. The Microscopic Agglutination Test (MAT) is considered as the "gold standard". In the test, acute and convalescent sera sample from a suspected patient is mixed with various live antigens from different serogroups of *Leptospira* organisms and is examined for agglutination reaction (Haake and Levett, 2015a and 2015b). A single titer of 1:100 (range from 1:100 to 1:800) or a fourfold rise in titer between acute and convalescent sera is indicative of serological confirmation of leptospirosis (WHO, 2003; Schreier *et al*., 2013; and Haake and Levett, 2015b). Although the test is superior in sensitivity and specificity over cultural methods, it has several limitations (Haake and Levett, 2015a). The test needs a panel of live organisms particular to the region from where the patient is suspected to have acquired the infection and also requires specialized and trained lab personnel which limits the diagnosis to only reference laboratories (Haake and Levett, 2015b). Furthermore, the antibody response necessary to conduct MAT test is usually insufficient for detection upto the second week of disease. Thus, to detect early host response during the first week of disease itself, several serologically-based methods have been developed. Among those, enzyme-linked immunosorbent assay (ELISA) is the most commonly used. ELISA utilizes a general Leptospiral antigen which detects IgM produced against pathogenic as well as non-pathogenic serogroups of *Leptospira* (WHO, 2003). ELISA has several advantages over MAT including greater sensitivity than MAT in the first week of infection, can be easily standardized and not restricted to be used only in reference laboratories (Lane and Dore, 2016).

As both cultural and serological methods are inadequate for early detection, advanced molecular techniques have been developed to aid early confirmatory detection. Even before the development of antibody response, conventional as well as real-time PCR techniques are highly sensitive for diagnosis of leptospirosis (Haake and Levett, 2015a). Blood is the most suitable clinical sample to detect *Leptospira* as hematogenous dissemination occurs during this period, but urine, CSF or tissue can have measurable levels in later phase of disease. Other techniques such as *in-situ* hybridization and loop mediated isothermal amplification have been described for early detection but the clinical applicability of these techniques is yet to be ascertained (Ahmed

et al., 2011). Thus currently, early detection of IgM immunoglobulins is probably the best one with rapid results with ease of use and cost effectiveness. Besides ELISA, other methods such as dipsticks, latex and slide agglutination tests and immunochromatography have been developed for rapid screening (WHO, 2003; Schreier *et al*., 2013; and Haake and Levett, 2015b). However, all positive tests need confirmatory testing, preferably with the MAT regardless of the method used of diagnosis (WHO, 2003).

TREATMENT

The initial treatment is decided according to the severity of the infection. Majority of cases of leptospirosis are mild and self-limiting, and patients often do not come for treatment (Hartskeerl and Wagenaar, 2015). Oral drugs such as doxycycline, azithromycin, amoxicillin or ampicillin are suitable for milder cases. Treatment should be given considering the cost, availability and differential diagnosis. Pregnant women and children should not be given doxycycline. Doxycycline or azithromycin are the drugs of choice where rickettsial diseases are endemic (Hartskeerl and Wagenaar, 2015). A typical Jarisch-Herxheimer reaction may develop within the first few hours after administration of antibiotic regardless of choice of antibiotic.

PREVENTION

Strategies for prevention of leptospirosis primarily depend on the awareness of epidemiology of leptospirosis and mechanism of transmission. Once the regional epidemiology and transmission risks have been identified, it is possible to alleviate the risks by taking measures to decrease exposure and implement prophylactic strategies such as immunization and pre or post exposure hemoprophylaxis.

Globally, human leptospirosis is associated with the poor housing standards and local infrastructure which exposes major population to rodent reservoirs. Rodenticides are useful on short term basis but they pose risks to children and wild animals. Construction of houses which prevents rodents from entering residential living areas should be built and it will help considerably reducing the risk of leptospirosis. Flood control strategies preventing inundation of residential areas will decrease the risk factors associated with leptospirosis.

Occupational contact with contaminated water or infected animals should be avoided. Use of personal protective equipment such as gloves, boots, goggles and overalls for workers involving in high risk occupations is important to prevent exposure of skin and mucous membrane. Water sports in endemic area and walking barefoot through flooded areas are specially considered is high risk activities.

Immunization of agricultural and companion animals with killed whole-cell vaccines is one of the key measure to reduce the source of infection and the risk of human leptospirosis infection. Humans can acquire infection vie exposure to animals which are acutely or chronically infected with leptospirosis and are shedding *Leptospira* in their urine.

CONCLUSION

Leptospirosis is a zoonotic infection that has a global distribution. The disease is caused by the Leptospira, a spirochete. Human leptospirosis is caused due to exposure to contaminated fresh water. Average incubation period is 7-12 days, however can vary from 2-30 days. Clinical

manifestations are asymptomatic but symptoms range from a mild, self-limiting febrile illness to fulminant renal and respiratory failure with high case fatality rate. Laboratory diagnosis can be challenging, particularly in resource deprived areas. Diagnosis is most commonly done by serological testing; however newer tests for quick and reliable diagnosis are becoming available. Oral doxycycline is the drug of choice for mild cases but azithromycin and oral penicillin can act as alternatives.

REFERENCES

1. Abdulkader R C (1997), "Acute Renal Failure in Leptospirosis", *Ren. Fail.*, Vol. 19, pp. 191-198.
2. Ahmed A, Grobusch M P, Klatser P and Hartskeerl R (2011), "Molecular Approaches in the Detection and Characterization of *Leptospira*", *J. Bacteriol. Parasitol.*, Vol. 3, pp. S5-002.
3. Bharti A R, Nally J E, Ricaldi J N, Matthias M A, Diaz M M, Lovett M A, Levett P N, Gilman R H, Willig M R, Gotuzzo E and Vinetz J M (2003), "Leptospirosis: A Zoonotic Disease of Global Importance", *Lancet Infect. Dis.*, Vol. 3, pp. 757-771.
4. Costa F, Hagan J E, Calcagno J, Kane M, Torgerson P, Martinez-Silveira M S, Stein C, Abela-Ridder B and Ko A I (2015), "Global Morbidity and Mortality of Leptospirosis: A Systematic Review", *PLoS Negl. Trop. Dis.*, Vol. 9, pp. e0003898.
5. Haake D A and Levett P N (2015a), "*Leptospira* Species (Leptospirosis)", in Bennett J E, Dolin R, Blaser J M (Eds.), *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th Edition, Saunders, Philadelphia, PA.
6. Haake D A and Levett P N (2015b), "Leptospirosis in Humans", *Curr. Top. Microbiol. Immunol.*, Vol. 387, pp. 65-97.
7. Hartskeerl R A, Collares-Pereira M and Ellis W A (2011), "Emergence, Control and Re-emerging Leptospirosis: Dynamics of Infection in the Changing World", *Clin. Microbiol. Infect.*, Vol. 17, pp. 494-501.
8. Hartskeerl R A and Wagenaar J P (2015), "Leptospirosis", in Longo D L (Ed.), *Harrison's Principles of Internal Medicine*, 19th Edition, McGraw-Hill, New York.
9. Helmerhorst H J, van Tol E N, Tuinman P R, de Vries P J, Hartskeerl R A, Grobusch M P and Hovius J W (2012), "Severe Pulmonary Manifestation of Leptospirosis", *Neth. J. Med.*, Vol. 70, pp. 215-221.
10. Katz A R, Ansdell V E, Effler P V, Middleton C R and Sasaki D M (2001), "Assessment of the Clinical Presentation and Treatment of 353 Cases of Laboratory-Confirmed Leptospirosis in Hawaii, 1974-1998", *Clin. Infect. Dis.*, Vol. 33, pp. 1834-1841.
11. Lane and Dore (2016), "Leptospirosis: A Clinical Review of Evidence Based Diagnosis, Treatment and Prevention", *World J. Clin. Infect. Dis.*, Vol. 6, pp. 61-66.
12. Leshem E, Meltzer E and Schwartz E (2011), "Travel-Associated Zoonotic Bacterial Diseases", *Curr. Opin. Infect. Dis.*, Vol. 24, pp. 457-463.
13. Nardone A, Capek I, Baranton G, Campèse C, Postic D, Vaillant V, Liénard M and Desenclos J C (2004), "Risk Factors for Leptospirosis in Metropolitan France: Results of a National Case-Control Study, 1999-2000", *Clin. Infect. Dis.*, Vol. 39, pp. 751-753.

14. Navinan M R and Rajapakse S (2012), "Cardiac Involvement in Leptospirosis", *Trans. R. Soc. Trop. Med. Hyg*., Vol. 106, pp. 515-520.

15. Pappas G, Papadimitriou P, Siozopoulou V, Christou L and Akritidis N (2008), "The Globalization of Leptospirosis: Worldwide Incidence Trends", *Int. J. Infect. Dis*., Vol. 12, pp. 351-357.

16. Schreier S, Doungchawee G, Chadsuthi S, Triampo D and Triampo W (2013), "Leptospirosis: Current Situation and Trends of Specific Laboratory Tests", *Expert Rev. Clin. Immunol*., Vol. 9, pp. 263-280.

17. Segura E R, Ganoza C A, Campos K, Ricaldi J N, Torres S, Silva H, Céspedes M J, Matthias M A, Swancutt M A, López Liñán R, Gotuzzo E, Guerra H, Gilman R H and Vinetz J M (2005), "Clinical Spectrum of Pulmonary Involvement in Leptospirosis in a Region of Endemicity, with Quantification of *Leptospira*l Burden", *Clin. Infect. Dis*., Vol. 40, pp. 343-351.

18. Taylor A J, Paris D H and Newton P N (2015), "A Systematic Review of the Mortality from Untreated Leptospirosis", *PLoS Negl. Trop. Dis*., Vol. 9, pp. e0003866.

19. "Update: Leptospirosis and Unexplained Acute Febrile Illness Among Athletes Participating in Triathlons—Illinois and Wisconsin, 1998", *MMWR Morb Mortal Wkly Rep,* 1998, Vol. 47, pp. 673-676.

20. "Update: Outbreak of Acute Febrile Illness among Athletes Participating in Eco-Challenge-Sabah 2000—Borneo, Malaysia, 2000", *MMWR Morb Mortal Wkly Rep,* 2001, Vol. 50, pp. 21-24.

21. Vijayachari P, Sugunan A P, Umapathi T and Sehgal S C (2001), "Evaluation of Darkground Microscopy as a Rapid Diagnostic Procedure in Leptospirosis", *Indian J. Med. Res*., Vol. 114, pp. 54-58.

22. WHO (2003), "Human Leptospirosis: Guidance for Diagnosis, Surveillance, and Control", WHO, Switzerland.

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