Leptospirosis

Abhijit Choudhary* Arun Baranwal**

*Senior Resident, **Professor, Division of Pediatric Critical Care, Advanced Pediatrics Center, PGIMER, Chandigarh, India

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Correspondence:

Dr. Arun Baranwal MD PG Diploma-Critical Care (UK), MAMS, FIAP, FRCPCH(UK) Professor, Division of Pediatric Critical Care, Advanced Pediatrics Center, PGIMER, Chandigarh, India. Phone: 7766908325. E mail: baranwal1970@gmail.com

ABSTRACT

Leptospirosis is a zoonotic infection with ubiquitous distribution caused by spirochete leptospira, and humans are incidental hosts. Leptospirosis is mostly reported during rainy season when there is freshwater flooding and water logging with poor sewage drainage. Leptospira are transmitted to humans by exposure to a water environment contaminated by urine of the infected animals. There are two distinct phases of leptospirosis, the initial “septicemic phase” due to leptospira mediated injury is closely followed by “immune phase”. Clinical symptoms include fever, headache, myalgia, vomiting, respiratory symptoms, and thus it is difficult to differentiate from other viral illnesses. Leptospira have a predilection for kidneys and causes acute tubular necrosis and interstitial nephritis. The sever form of Leptospirosis is characterized by hepatic, respiratory and renal dysfunctions, hemorrhagic manifestations, cardiovascular collapse and CNS dysfunction. Microscopic Agglutination Test (MAT) is the gold standard for diagnosis, however ELISA is a pragmatic alternative to MAT for confirming the diagnosis. Majority (90%) of leptospirosis cases are mild and can resolve spontaneously. Early initiation of antimicrobials can lead to faster recovery and may prevent from progression to severe leptospirosis. Penicillin, oral or intravenous, are the first lines of therapy. Supportive care is of utmost importance for management of leptospirosis and associated organ dysfunctions.

Key Words: Leptospirosis, Children, Critical Care.
Introduction:

Leptospirosis is a zoonotic infection with ubiquitous distribution caused by spirochete leptospira, and humans are incidental hosts. Leptospirosis in children result in wide variety of clinical manifestations ranging from subclinical infection resembling other viral illnesses to a more severe form termed as “Weil Syndrome/Disease” or “Icteric Leptospirosis”. It is characterized by hepatic and renal dysfunction, hemorrhagic manifestations, cardiovascular collapse, CNS dysfunction with a high mortality.1

Epidemiology:

Leptospirosis is an occupational disease and is increasingly being reported with occupations associated with outdoor activities in contaminated water.2-4 Leptospirosis is mostly reported during rainy season when there is freshwater flooding and water logging with poor sewage drainage. Annual incidence is estimated from 0.1-1 per 100,000 in temperate climates to 10-100 per 100,000 in the humid tropics. Incidence of more than 100 per 100,000 is encountered during outbreaks and in high-exposure risk groups. High endemic regions are South Asia, Southeast Asia, Central and South America, Caribbean and Pacific Islands. In India, cases are mostly reported from coastal regions of Gujrat, Maharashtra, Karnataka, Kerala, Tamilnadu, Andhra Pradesh, Andaman and Nicobar, and Orissa.5,15 It assumes epidemic potential during floods in these provinces.

Transmission to humans:

There are seven distinct species of pathogenic leptospira and more than 200 serological variants (serovars), Leptospira interrogans being the most common species pathogenic to humans.1 Leptospira infect many mammals like rats, rodents, cats, dogs, cattle, pigs, foxes, jackals, mongooses, raccoons, bandicoots etc., and humans represent the dead end in the chain of transmission. Among these mammals, rats and rodents are the most important reservoirs worldwide. Leptospira are transmitted to humans either by contact with blood, urine, tissues, or organs of infected animals or by exposure to an environment that has been contaminated by them; urine being the most important as Leptospira are excreted in the urine of infected animals for prolonged time. And thus, freshwater / water-logged areas / waterbodies contaminated by urine of rats is the most important vehicle of transmission.6-8

Pathogenesis:

Leptospira enter human body via lungs through aerosol droplets, skin breaks, mucous membranes and conjunctival membranes causing sub-clinical infection or overt disease. Post entry, leptospira invades lymphatic system and bloodstream and spreads rapidly throughout the body. Due to slow growth of Leptospira, clinical manifestations appear after incubation period of 5-14 days (range, 2-30 days). There are two distinct phases of leptospirosis, the initial phase “septicemic phase” is due to leptospira mediated injury and “immune phase” occurs due to activation of host immune response. Leptospira cause widespread endotheliopathy and capillaritis possibly by endotoxin release leading to capillary leaks and hemorrhagic diathesis. Bleeding in these patients is also attributed to depletion of serum prothrombin, thrombocytopenia or both.9 Patients have widespread hepatocellular injury leading to hepatic dysfunction. Jaundice is contributed by intravascular
hemolysis as well.\textsuperscript{10} Lung involvement is predominantly due to hemorrhage; severe cases may have massive hemoptysis. Haemorrhagic pneumonitis with interstitial and intra-alveolar haemorrhages surrounded by focal capillary injury are common pathologic changes.\textsuperscript{12} Leptospira have a predilection for kidneys and cause acute tubular necrosis and interstitial nephritis. Respiratory and Renal failure are the leading causes of death in these patients.\textsuperscript{11} Patients with severe leptospirosis have evidence of a “cytokine storm” with higher levels of IL-6, TNF-alpha and other cytokines compared to those with milder disease.\textsuperscript{12} Patients may develop meningitis which is due to deposition of antigen-antibody complexes rather than due to leptospira directly.

**Clinical Features:**

Leptospirosis is systemic infection, characterized by extensive vasculitis with varied presentation. The incubation period is generally 5-14 days (range, 2-30 days).\textsuperscript{1} Both anicteric and icteric leptospirosis follow a biphasic course.

**Anicteric Leptospirosis**

Majority (~90%) of patients with leptospirosis are anicteric. During the first stage (septicemic stage), patients have abrupt appearance of fever, chills, vomiting, headache, severe myalgia restricting mobility; these symptoms may last for 4-7 days. This stage is difficult to differentiate from a viral illness. Physical examination during this septicemic stage may reveal conjunctival suffusion, erythematous macular / maculopapular rash, petechiae, purpura, generalized muscle tenderness, generalized lymphadenopathy and hepatosplenomegaly. Chest radiograph may reveal confluent infiltrates, consolidation or small patchy snowflake like lesions in the periphery of lung fields. Patient may become asymptomatic for 1-3 days, and this symptomatic improvement coincides with disappearance of leptospires from blood, CSF and other tissues. It is followed by reappearance of fever heralding the onset of second stage (immune stage), which may last from 4-30 days. This stage is characterized by rash, headache, meningitis and uveitis. Other manifestations include disproportionate tachycardia with myocarditis, polyserositis, encephalitis. Lumbar puncture during the immune stage may reveal CSF pleocytosis with or without meningeal symptoms or signs.

**Icteric Leptospirosis (Weil Syndrome)**

Weil syndrome is severe form of leptospirosis which occurs in less than 10% of patients, and is characterized by jaundice, severe encephalopathy, shock and renal failure. Jaundice is the hallmark of Weil syndrome with conjugated hyperbilirubinemia with usual bilirubin concentration <20 mg/dL. There is minimal elevation of aspartate and alanine aminotransferases with values rarely exceeding 100-200 IU/dL respectively. Widespread vasculitis causes third spacing of fluids; patients may present with or develop hypovolemic shock later. Respiratory involvement is characterized by cough, chest pain and blood-tinged sputum. Severe cases may present with hemoptysis, rapidly progressive respiratory distress and respiratory failure. Patients initially have basal crepts which may rapidly spread upwards. Chest radiograph shows basal and mid zone opacity. It is the commonest cause of early death during first few days. Renal dysfunction usually occurs during the first week, worsens until end of second week, starts improving thereafter with complete recovery by the end of fourth week provided patient is maintained on renal replacement therapy.\textsuperscript{15} Usually, there is no residual renal dysfunction. If left untreated, renal dysfunction is the
commonest cause of late mortalities.\textsuperscript{13} Patients may develop features of myocarditis, with cardiac arrhythmias, supraventricular tachyarrhythmia and atrioventricular blocks being common. Ventricular tachyarrhythmias are infrequent. Meningoencephalitis, radiculitis and peripheral neuropathy have also been reported. Hyponatremia is a consistent finding in patients with severe icteric leptospirosis. Other biochemical abnormalities that occur are hypokalemia, thrombocytopenia and elevated prothrombin time.

**Differential Diagnosis:**

Tropical infections that closely resemble leptospirosis and are prevalent in the same regions where leptospirosis is endemic are viral hepatitis, malaria, dengue fever / dengue hemorrhagic fever, scrub typhus, enteric fever and acute encephalitis syndrome. Possibility of co-infections should always be considered due to similar epidemiology of these diseases. Icteric leptospirosis should be differentiated from fulminant hepatitis due to Hepatitis A and Hepatitis E viruses. Differentiating features are mildly elevated liver enzymes, features of capillary leak, thrombocytopenia and acute renal failure early in the course of illness in Leptospirosis as against viral hepatitis. Also, creatinine phosphokinase levels may be elevated in the former unlike in viral hepatitis patients.\textsuperscript{14}

**Case Definitions** - National Centre for Disease Control (NCDC), India have given following case definitions for management of leptospirosis.\textsuperscript{15}

**Suspected Leptospirosis:** Acute febrile illness with headache, myalgia and prostration associated with a history of exposure to infected animals or an environment contaminated with animal urine with one or more of the following:

1. Calf muscle tenderness
2. Conjunctival suffusion
3. Jaundice
4. Anuria / oliguria, and/or proteinuria
5. Hemorrhagic manifestations (intestines, lung)
6. Meningeal Irritation
7. Nausea, Vomiting, Abdominal pain, Diarrhea

**Probable Leptospirosis:** Clinically suspected case with one of the following presumptive laboratory tests being positive:

- A positive result in immune assay based rapid diagnostic tests, e.g., slide agglutination test / latex agglutination test / immunochromatographic test
- A Microscopic Agglutination Test (MAT) titer of 100/200/400 or above in single sample based on endemicity
- Microscopic demonstration of leptospires directly or by staining methods in blood, CSF and/or urine

**Confirmed Leptospirosis:** A suspect / probable case with one of the following confirmatory laboratory tests being positive:
- Isolation of leptospires from clinical specimen on culture of blood, CSF and/or urine
- Four-fold or greater rise in the MAT titer between acute and convalescent phase serum.
- Positive rapid diagnostic test followed by positive ELISA.
- Positive PCR test.

**Laboratory Diagnosis:**

The initial investigations required in a suspected case of leptospirosis are complete blood count with peripheral smear, ESR, electrolytes, renal function tests and urine routine examination. Patient may have anemia, polymorphonuclear leucocytosis and thrombocytopenia. Peripheral smear may reveal toxic granules. Icteric leptospirosis may have hyperbilirubinemia with mildly elevated transaminases (usually in hundreds). Acute inflammatory markers like CRP and procalcitonin may be elevated along with ESR. Patients may have markedly elevated creatine phosphokinase suggesting presence of myositis. Urine routine may reveal hematuria, proteinuria and casts.

**Serological tests:**

Leptospira can be cultured from blood, urine, CSF and most tissues during the septicemic stage of illness which lasts for 4-7 days after which the circulating antibodies appear during the immune phase. However, leptospirosis can last for few weeks.

The various serologic tests available for diagnosis of leptospirosis are microscopic agglutination test (MAT), enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination assay. Microscopic agglutination test (MAT) is the gold standard for diagnosis in which live antigens are used from common endemic leptospira serovars (>200 serovars). A single titer should be interpreted in the background of degree of endemicity present in the region. Four-fold or greater rise in the titer between acute and convalescent phase serum confirms the diagnosis. The test is time consuming and potentially hazardous to laboratory workers, however it is an important epidemiological tool for serovar identification.

ELISA IgM is pragmatic alternative to MAT for the presumptive diagnosis of leptospirosis due to its simplicity, sensitivity and potential of standardization. It requires just one genus-specific antigen which is shared by all serovars. However, it is less specific and weak cross reactions with other diseases may occur. Slide agglutination test is equivalent to ELISA IgM, is inexpensive, can easily and rapidly be performed at bedside. Indirect hemagglutination assays are less sensitive and specific compared to ELISA. Some of these tests are made available at the primary and secondary healthcare centers in the regions with high endemicity, and referral diagnostic laboratories have been established at Delhi, Surat, Ahmedabad, Bengaluru, Madurai, Chennai, Port Blair, Izatnagar (UP) and Gwaliar by the Government of India.

**Management**

Majority of leptospirosis cases are mild and can resolve spontaneously. Early initiation of antimicrobials can lead to faster recovery and may prevent progression to severe leptospirosis. Antimicrobials should be started as early as possible and before the invading organisms damage
endothelium as after day 10 of illness organism disappears from blood and CSF with appearance of antibodies. However, antimicrobial therapy should not be denied even after 10 days.

Diagnosis of leptospirosis is suspected based on presenting symptoms and signs, risk factors and exposure history. Rapid diagnostics tests can aid in diagnosis but negative result does not rule out early infection. A suspected, probable or confirmed case of leptospirosis should be treated with antimicrobials, Penicillins being the first line therapy. In a randomized double-blind trial, intravenous crystalline penicillin (for 7 days) was shown to be effective in severe leptospirosis as it significantly reduced duration of fever, length of hospitalization, improved renal functions and prevented leptospiral shedding in urine. It was effective even when the therapy was initiated late during illness. However, this positive effect of intravenous crystalline penicillin (5 days) was negated by another placebo-controlled trial among patients with icteric leptospirosis. Suputtamongkol et al. in their open randomized controlled trial evaluated effect of three antimicrobials (penicillin, cefotaxime and doxycycline) on leptospirosis, and they did not find any significant difference in terms of time to defervescence and length of hospitalization between the three treatment groups. Azithromycin (for 3 days) was not found to be inferior to Doxycycline (for 7 days) in the treatment of leptospirosis. Recommendations from National Center for Disease Control (India) for the treatment of leptospirosis with organ dysfunction(s) are as follows:

1. **Without organ Dysfunction**
   - Children <8 years: Oral Amoxicillin/ Ampicillin for 7 days
   - Children >8 years: Oral Doxycycline for 7 days (as in adults)

2. **With organ Dysfunction**
   - Inj. Crystalline penicillin, 2–4 lacs IU/Kg/ day for 7 days.
   - Alternative regimes for individuals sensitive to penicillin group of drugs:
     - Intravenous Ceftriaxone 50-75 IV mg/kg/day for 7 days  OR
     - Intravenous Cefotaxime 50-100 IV mg/kg/day for 7 days OR
     - Intravenous Erythromycin 30-50mg/kg/day in divided dose for 7 days

**Supportive Care**

Supportive care is of utmost importance for management of leptospirosis, characterized by organ support measures applicable to any critically ill patients with multi-organ dysfunction. Prompt and specific treatment is required for dehydration, shock (hypovolemic, distributive, cardiogenic), acute respiratory and renal failure. Maintaining euvolemma and normal electrolyte balance is important. Renal failure can be prevented by ensuring optimal circulatory volume. Anecdotal reports suggest role of corticosteroids in patients with profound shock. Leptospirosis causes a non-oliguric and hypokalemic form of acute kidney injury; however, patients can develop oligo-anuric acute kidney injury due to acute tubular necrosis. Peritoneal dialysis or hemodialysis may be required for renal failure. Other renal replacement measures have also been tried successfully. High-dose corticosteroid has been used for treatment of immune-complex mediated renal failure, but its role is not fully established. Liver failure should be managed with supportive care. Plasma exchange with hemodiafiltration may have a role in patients with severe hyperbilirubinemia and oligo-anuric acute kidney injury.
Conclusions

Leptospirosis is a zoonotic disease common in the rainy season characterized by febrile illness, myalgia, headache, conjunctival congestion, skin rashes, respiratory symptoms, and non-oliguric kidney injury mimicking a viral illness. Its severe form is characterized by jaundice, respiratory distress, oligo-anuric renal failure with multiorgan dysfunction syndrome. Early clinical suspicion and early administration of antimicrobial are essential to prevent progression to severe form and limiting complications of severe leptospirosis. The latter is recommended to be treated with intravenous crystalline penicillin and supportive care in critical care setting.

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References:


