

Chapter 7

Indian Guidelines for the Diagnosis and Management of Human Leptospirosis

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INTRODUCTION

Leptospirosis has been under reported and under diagnosed from India due to a lack of awareness of the disease and lack of appropriate laboratory diagnostic facilities in most parts of the country. Combining clinical expertise and awareness with confirmatory laboratory back up dramatically increases the recognition of patients with leptospirosis. Clinical features of leptospirosis vary from mild illness to severe life-threatening illness. Leptospirosis can be diagnosed only by laboratory tests as the clinical features are nonspecific. But the laboratory tests are complex and hence definite guidelines for diagnosis of human leptospirosis is necessary.¹

The incidence of leptospirosis in developing countries is 10-100/1,00,000 cases per year. By this estimate, India should report 0.1-1.0 million cases per year, but less than 10,000 cases are reported. Only four states (Kerala, Gujarat, Tamil Nadu and Maharashtra) report more than 500 cases per year. Andaman, Andhra Pradesh, Assam, Goa, Delhi, Karnataka, Orissa, Puducherry and Uttar Pradesh also report cases.^{1,2} Kerala has reported leptospirosis cases from all districts and this disease is the leading cause of mortality, among the infectious diseases. Gujarat has reported cases from the southern districts of Surat, Valsad and Navasari.² Chennai and Mumbai are large cities from which leptospirosis has been reported. Recently, West Bengal, Punjab, Haryana and Himachal Pradesh have reported cases of leptospirosis.³⁻⁵

The following guidelines for the management of human leptospirosis would be discussed:

- Guidelines for clinical and laboratory diagnosis of human leptospirosis.
- Guidelines for treatment of human leptospirosis.

The guidelines for prevention and control of leptospirosis are not discussed in this chapter as this is a zoonosis and requires a multidisciplinary approach involving various other departments.

GUIDELINES FOR CLINICAL AND LABORATORY DIAGNOSIS OF HUMAN LEPTOSPIROSIS

The following guidelines are available in India for diagnosis of leptospirosis:

- Faine's criteria [World Health Organization (WHO) guidelines 1982].⁶
- Modified Faine's criteria (2004).⁷
- Modified Faine's criteria with amendment (2012).
- Guidelines by the Regional Medical Research Center (ICMR) and WHO regional office for South-East Asia.^{2,8}
- Guidelines for prevention and control of leptospirosis: National Institute of Communicable Diseases (Zoonosis Division) 2006.⁹

Faine's Criteria (WHO Guidelines 1982)

In these guidelines, the diagnosis is based on three categories viz. clinical data (Part A), epidemiological factors (Part B) and bacteriological and lab findings (Part C).⁶ A score of A + B + C = 25 or more is diagnostic of leptospirosis (**Table 1**). The laboratory findings are based on culture and microscopic agglutination test (MAT). The MAT is based on endemicity and also includes low titers. Seroconversion and fourfold raise have been given the highest score. These criteria can, therefore, be used only in centers which have facilities to do culture and MAT. In addition, the titer levels of MAT have not been defined.

AM Bal et al. in their study utilizing Faine's criteria have observed that sensitivity, specificity, positive predictive value and negative predictive value to be 81.8%, 72.9%, 40.9% and 94.5% respectively.¹⁰

Modified Faine's Criteria (2004)

This criteria has been modified from the original WHO criteria (Faine's criteria).⁶ The most important modification has been made in the diagnostic criteria, where simple and easily available tests such as Elisa and macroscopic slide agglutination test (MSAT) have been included in addition to MAT and culture (**Table 2**). The original criteria had included only MAT, which is a complicated test and is not easily available. The significance of various diagnostic tests for diagnosis of leptospirosis is shown in **Table 3**.

In addition, as Leptospiral cases are reported after rainfall, this factor has been included in the epidemiological criteria (**Table 4**). For example, a patient with fever + rainfall and contact with contaminated environment + positive Elisa would have a score of 26 which would be diagnostic of acute leptospirosis.

The modified Faine's criteria have two objectives: (1) Confirmation of leptospirosis utilizing laboratory tests. The clinical features of leptospirosis are nonspecific and hence confirmation by diagnostic tests is essential. Simple rapid tests such as Elisa and MSAT have been included along with MAT and cultures to confirm the diagnosis with appropriate scores (A + B + C = 25 or more). This is the most important aspect of the criteria. It is very important that rapid tests are made easily available in both urban and rural hospitals. (2) Since these tests become positive only after a week, a scoring based on clinical and epidemiological criteria has been used for the first week (A + B = 26 or more). This scoring system is valuable in diagnosis of severe leptospirosis. But this has less sensitivity than A + B + C as milder cases tend to be missed.⁷ Therefore, it is very essential that investigations to diagnose leptospirosis are definitely done. The A + B criteria should be used to start empiric therapy even for possible leptospirosis (A + B = 20 - 25). It is essential to combine both clinical

TABLE 1 | Faine's criteria (1982)

Clinical data (Part A)	Epidemiological factors (Part B)	Bacteriological and laboratory findings (Part C)
Headache	2	<i>Isolation of leptospira in culture—Diagnosis certain</i> Positive serology (MAT) <i>Leptospirosis endemic</i> Single positive—Low titer Single positive—High titer Leptospirosis nonendemic
Fever	2	
Temperature >39°C	2	
Conjunctival suffusion	4	
Meningism	4	
Muscle pain	4	
Conjunctival suffusion + Meningism + Muscle pain	10	
Jaundice	1	
Albuminuria/Nitrogen retention	2	
Total score		
Presumptive diagnosis of leptospirosis is made of: Part A or Part A and Part B score : 26 or more Parts A, B, C (Total) : 25 or more A score between 20 and 25 suggests leptospirosis as a possible diagnosis.		

Abbreviation: MAT, Microscopic agglutination test

TABLE 2 | Modified Faine's criteria (2004)

Clinical data (Part A)	Epidemiological factors (Part B)	Bacteriological and laboratory findings (Part C)
Headache	2	<i>Isolation of leptospira in culture—Diagnosis certain</i> Positive serology Elisa IgM positive* SAT—Positive* MAT—Single high titer* MAT—Rising titer/ seroconversion (paired sera) Total * Any one of the tests only should be scored
Fever	2	
Temperature >39°C	2	
Conjunctival suffusion	4	
Meningism	4	
Muscle pain	4	
Conjunctival suffusion + Meningism + Muscle pain	10	
Jaundice	1	
Albuminuria/Nitrogen retention	2	
Total score		
Presumptive diagnosis of leptospirosis is made of: Part A or Part A and Part B score : 26 or more Parts A, B, C (Total) : 25 or more A score between 20 and 25 suggests leptospirosis as a possible diagnosis.		

Abbreviations: MAT, Microscopic agglutination test; SAT, Slide agglutination test

features and epidemiological risk factors to make a possible diagnosis of leptospirosis. For example, a patient with fever, headache, myalgia and conjunctival suffusion during the monsoon month who gives the history of wading through flood water would have a score of 21 which would be diagnostic of possible leptospirosis. Therefore, in the first week clinical and epidemiological factors (A + B) should be used to diagnose leptospirosis, while in the second week, laboratory tests should be used to confirm the diagnosis.¹

Sethi et al. from PGI, Chandigarh had utilized modified Faine's criteria in their study of leptospirosis and have recommended that this criteria can be utilized as a useful guide for diagnosis of leptospirosis by clinicians.³ Chauhan et al. from Himachal Pradesh in their study of 13 patients of leptospirosis have stated that only 7 out of 13 can be diagnosed by Faine's criteria but all 13 cases could be diagnosed by modified Faine's criteria.⁴ ND Mandal et al. from Kolkata have also utilized modified Faine's criteria in the diagnosis

TABLE 3 | Role of diagnostic tests for leptospirosis

Culture	PCR	MAT	MSAT/Elisa IgM and other rapid screening tests
<ul style="list-style-type: none"> Isolation of leptospira organism by culture of blood, CSF and urine are the most definite way of confirming leptospirosis Culture does not contribute to an early diagnosis as results come late, weeks or even months after inoculation of culture medium. 	<ul style="list-style-type: none"> PCR is the only available diagnostic test available in the first week of leptospirosis It is a complicated and expensive test The serovar cannot be identified by this test 	<ul style="list-style-type: none"> Gold standard Complicated, DFM required Titers peak late (2nd or 3rd week), but persist longer (5 to 10 years) Valuable in sero epidemiologic studies Less sensitive for current diagnosis Repeat samples required for confirming diagnosis Requires 24 live serogroup cultures Cut-off titers controversial <p>Interpretation of MAT</p> <ul style="list-style-type: none"> Single titer <ul style="list-style-type: none"> 1:100—significant criteria Diagnostic criteria <ul style="list-style-type: none"> Endemic area—1:400 (1:800, 1:1,600) Nonendemic area—1:100, 1:200 Serosurvey—1:50 Repeat titer <ul style="list-style-type: none"> Four-fold rise/seroconversion 	<ul style="list-style-type: none"> Single positive sample adequate for diagnosis Simple, sensitive and specific tests Becomes positive earlier than MAT Cannot identify the serogroup Can be done also in small rural hospitals Can be easily done for a large number of patients during an epidemic <p>Other rapid tests are:</p> <ul style="list-style-type: none"> Latex agglutination test Lepto dipstick Lepto tek lateral flow Lepto tek Dri-Dot test

Abbreviations: CSF, Cerebrospinal fluid; PCR, Polymerase chain reaction; MAT, Microscopic agglutination test; MSAT, Macroscopic slide agglutination test

TABLE 4 | Epidemiological risk factors

Environmental risk factors	Occupational risk groups	Recreational activities
<ul style="list-style-type: none"> Rainfall and flooding Contaminated environment <ul style="list-style-type: none"> Poor sanitation Inefficient solid waste disposal Inadequate drainage facilities and open drains Presence of rodents, cattle, pigs and dogs Walking bare foot Wading through contaminated water Absence of indoor toilets Living in overcrowded residential areas (urban slums) Outdoor manual work. 	<ul style="list-style-type: none"> Farmers <ul style="list-style-type: none"> Rice, sugarcane, vegetables, cattle, pigs Sewage workers Abattoir workers, butchers Veterinarians, laboratory staff Miners Fishermen—Inland Soldiers 	<ul style="list-style-type: none"> Swimming in fresh water Sailing Marathon runners Gardening Adventure travel Water sports Ecotourism

of 214 cases of leptospirosis.⁵ Toyakawa et al. have stated that the modified Faine's criteria have produced statistically higher specificity and positive predictive values than those of standard Faine's criteria. These criteria have high negative values which may help to exclude leptospirosis from the differential diagnosis of febrile patients.¹¹⁻¹⁵ Other workers have also utilized modified Faine's criteria to diagnose leptospirosis.¹⁶⁻¹⁹

Modified Faine's Criteria (with Amendment) 2012

Certain additions have been made to the modified Faine's criteria 2004 to make it more user friendly (Table 5).

- Since pulmonary hemorrhage is an important complication, hemoptysis and dyspnea have been included in the clinical criteria.
- Since many other rapid tests have become available, they have been included in the laboratory criteria.²⁰⁻²⁸

TABLE 5 | Modified Faine’s criteria (2012)

Clinical data (Part A)	Epidemiological factors (Part B)	Bacteriological and laboratory findings (Part C)			
Headache	2	Rainfall	5	Isolation of leptospira in culture—Diagnosis certain	
Fever	2	Contact with contaminated Environment	4	PCR	25
Temperature >39°C	2			Positive serology	
Conjunctival suffusion	4	Animal contact	1	Elisa IgM positive*	15
Meningism	4	Total	10	SAT-Positive*	15
Myalgia	4			Other rapid tests**	15
Conjunctival suffusion + Meningism + Myalgia	10			MAT- Single positive in high titer*	
Jaundice	1			MAT - Rising titer/seroconversion (paired sera)	15
Albuminuria/Nitrogen retention	2			* Any one of the tests only should be scored	25
Hemoptysis/Dyspnea	2			** Latex agglutination test/Lepto dipstick/Lepto Tek lateral flow/Lepto Tek Dri-Dot test	
Presumptive diagnosis of leptospirosis is made of:					
Part A or Part A and Part B score : 26 or more					
Parts A, B, C (Total) : 25 or more					
A score between 20 and 25 suggests leptospirosis as a possible diagnosis.					

Abbreviations: PCR, Polymerase chain reaction; MAT, Microscopic agglutination test; SAT, Slide agglutination test

- Since polymerase chain reaction (PCR) is available for diagnosis of leptospirosis in the first week, this has been included in the diagnostic criteria.²⁷⁻²⁸

Guidelines of the Regional Medical Research Center (ICMR) and WHO Regional Office for South-East Asia^{2,8}

Case Definition

Considering the changing clinical manifestation of leptospirosis, limitation of available diagnostic test methods and need of early case detection and early treatment, the following case definition has been adopted. In these guidelines, the case definition has three categories:

1. *Suspect*: Which consists of only clinical features
2. *Probable*: Which consists of clinical features + Rapid diagnostic tests
3. *Confirmed*: Which consists of clinical features + positive MAT/PCR/Culture.

Suspect

- Acute febrile illness (≥ 38.5°C) and/or severe headache with:
 - Myalgia
 - Prostration and/or
 - Conjunctival suffusion
 - History of exposure to leptospira-contaminated environment.

Probable

Probable (At primary health care level)

- Suspect case with any two of the following:
 - Calf tenderness
 - Cough with or without hemoptysis
 - Jaundice
 - Hemorrhagic manifestations
 - Meningeal irritation
 - Anuria/oliguria and/or proteinuria
 - Breathlessness

- Cardiac arrhythmias
- Skin rashes.

Probable (At Secondary and Tertiary Health Care Levels)

- Based on availability of laboratory facilities a probable case of leptospirosis is a suspect case with a positive rapid IgM test. And/Or Supportive serologic findings (i.e. a MAT titer equal to 200 in a single sample) And/Or Any three of the following:
 - *Urinary findings*: Proteinuria, pus cells, blood
 - Relative neutrophilia (> 80%) with lymphopenia
 - Platelets less than 100,000/cu mm
 - Elevated serum bilirubin more than 2 mg%; liver enzymes moderately raised (Serum alkaline phosphatase, S amylase, CPK).

Confirmed

A confirmed case of leptospirosis is a suspect or probable case with any one of the following:

- Isolation of leptospire from clinical specimens
- Positive PCR result
- Seroconversion from a negative to positive or fourfold rise in titer by MAT
- Titer by MAT of 400 and greater in a single sample. Where laboratory capacity not well established: Positive by two different rapid diagnostic tests could be considered as laboratory confirmed case.

Guidelines for Prevention and Control of Leptospirosis: National Institute of Communicable Diseases (Zoonosis Division) 2006⁹

This includes only two categories viz. suspect and confirmed. A confirmed case is a suspect case with positive laboratory report.

Case Classification

Suspect: Acute febrile illness with headache, myalgia and prostration associated with any of the following:

- Conjunctival suffusion
- Meningeal irritation
- Anuria or oliguria and/or proteinuria
- Jaundice
- Hemorrhages (from the intestines; lung bleeding is notorious in some areas)
- Cardiac arrhythmia or failure
- Skin rash and a history of exposure to infected animals or an environment contaminated with animal urine.
- Other common symptoms include nausea, vomiting, abdominal pain, diarrhea, arthralgia.

Confirmed: A suspect case with positive laboratory test.

The diagnostic tests to be carried out at different health facilities are as follows:

CHC/District Hospitals

- Detection of IgM antibodies against leptospire by rapid screening tests (to be confirmed by MAT).
- The following abnormal laboratory changes are observed.
 - Total WBC count slightly elevated with neutrophilia
 - Increased erythrocyte sedimentation rate (about 60 mm)
 - Thrombocytopenia
 - Increased BUN and serum creatinine
 - Sodium potassium—normal or slightly reduced
 - Urine analysis for proteinuria, hematuria and casts
 - Increase in serum bilirubin (predominantly direct) levels
 - Alkaline phosphatase, SGOT and SGPT moderately elevated
 - Marked elevation in serum creatinine phosphokinase (CK) and MB variant.

Endemic States/Tertiary Level Health Care Facility

- Elisa
- Microscopic agglutination test (MAT)
- Isolation
- PCR.

The WHO had contributed to the various guidelines discussed above (except the modified Faine's criteria, which was modified from the original WHO guidelines to suit Indian institutions). The guidelines which insist on culture, MAT and PCR for confirming diagnosis are not practical for India, as they are not easily available in most institutions. In addition, a single MAT titer more than or equal to 1:400 has been included as a test to confirm diagnosis. Seroconversion and fourfold rise in MAT titer are acceptable for confirming diagnosis. But, single high titer in MAT is controversial as high titers can persist for a long time and hence it should be classified under probable case definition. Elisa IgM and other rapid tests are simple, sensitive and specific test for the diagnosis of leptospirosis, but they are categorized as probable cases. These tests are considered as screening tests only. Therefore, the modified Faine's criteria which include Elisa IgM and other rapid tests along with culture and MAT for diagnosis of leptospirosis is the more practical guideline for Indian institutions. If MAT is available as a single test, positive rapid tests plus high titers in MAT can confirm the diagnosis of current leptospirosis. A negative rapid test with positive MAT might suggest past infection.¹³

Leptospirosis can occur in both urban and rural areas. The rapid tests for diagnosis of leptospirosis should be made available in taluk/district hospitals and the microbiology departments of medical college hospitals in the various districts. The MAT should be made available in the leptospirosis laboratory (which could be a part of the

microbiology laboratory of the premier government medical college hospital of the State). The PCR and culture should be available in the reference laboratories of the country. Samples which are obtained from suspect patients should be sent from the smaller laboratories in the taluk and district headquarter hospitals to the leptospirosis laboratory/reference laboratory for MAT, culture and PCR.^{6,20}

GUIDELINES FOR MANAGEMENT OF HUMAN LEPTOSPIROSIS

Leptospirosis is diagnosed to be mild if a patient with acute febrile illness has no complications and can take oral drugs. Mild leptospirosis can be managed in an outpatient setting. Leptospirosis is considered to be severe, if a patient has acute febrile illness with complications. Patient with severe leptospirosis should be admitted and managed in hospital. The complications of leptospirosis are shown in **Table 6**.

The differential diagnosis of leptospirosis is shown in **Table 7**.

The relevant investigations to be done are shown in **Table 8**.

Antibiotic therapy should be started as soon as the diagnosis is suspected regardless of the duration of symptoms.²⁰ It is not

TABLE 6 | Complications of leptospirosis

- Jaundice
- Acute kidney injury
- Pulmonary hemorrhage
- ARDS
- Neuroleptospirosis
- Hypotension
- Thrombocytopenia
- Myocarditis
- Ocular complications
- Hypokalemic paralysis

Abbreviation: ARDS, Acute respiratory distress syndrome

TABLE 7 | Differential diagnosis of leptospirosis

- Malaria
- Dengue
- Typhoid
- Tuberculosis
- Scrub typhus
- Influenza
- Pneumonia
- Urinary tract infection
- Sepsis
- Viral hepatitis

TABLE 8 | Investigations for leptospirosis

- Urine analysis
- TC/DC/ESR/Hb/Platelet count
- Sr bilirubin/SGOT/SGPT
- Plasma urea, creatinine and electrolytes
- Chest X-ray
- Arterial blood gas (ABG) analysis
- ECG
- Tests for diagnosis of leptospirosis

Abbreviations: SGOT, Serum glutamic-oxaloacetic transaminase; SGPT, Serum glutamic-pyruvic transaminase

TABLE 9 | Management of leptospirosis

- **Mild leptospirosis**
 - Doxycycline 100 mg bd for 7–10 days
 - Amoxicillin 500 mg qid for 7–10 days
 - Ampicillin 500–750 mg qid for 7–10 days
 - Azithromycin 500 mg od for 3 days
- **Severe leptospirosis**
 - Penicillin 1.5 million units IV qid for 7 days
 - Ceftriaxone 1 g IV od for 7 days
 - Start treatment before 5 days
 - Empiric therapy recommended (WHO)
- **Fluid therapy**
 - Indication: Hypovolemia/Hypotension/Hemorrhage
 - Fluids: IV saline/Blood transfusion
- **Acute kidney injury**
 - Mild: Fluid therapy/Diuretics
 - Severe: Dialysis
- **ARDS/Pneumonia**
 - Ventilatory support

Abbreviations: ARDS, Acute respiratory distress syndrome; WHO, World Health Organization

necessary to confirm the diagnosis or wait for the results of the tests before starting treatment, as the clinical profile and environmental history are more important. This is because early recognition and treatment (< 5 days) is more important to prevent complications. But in the second week the diagnosis should definitely be confirmed.¹

Mild leptospirosis can be treated with oral doxycycline, azithromycin, amoxicillin and ampicillin and severe leptospirosis can be treated with IV penicillin or ceftriaxone. The management of leptospirosis is shown in **Table 9**.

Recommendations for Management Based on the Availability of Diagnostic Facilities in Centers where no Diagnostic Facilities are Available (Rural Areas)

The common causes of acute febrile illnesses are malaria, leptospirosis, dengue, scrub typhus and viral respiratory diseases. It is difficult to diagnose these illnesses without laboratory facilities. In addition, leptospirosis co-infection can occur with malaria, scrub typhus, viral hepatitis and dengue.^{29–35} It is recommended that all febrile patients can be treated with doxycycline and chloroquine which is the empiric therapy for malaria, scrub typhus and leptospirosis.⁹ If there is organ dysfunction and/or fever persists, they should be transferred to higher centers for further management.

In Centers where Diagnostic Facilities are Available

Even in centers with laboratory facilities, empiric therapy is recommended for leptospirosis where the disease is endemic, since serological tests become positive only after 1 week (unless PCR is available). Mild cases can be treated with chloroquine and doxycycline and severe cases with IV crystalline penicillin or ceftriaxone/quinine or artemisinin and doxycycline. If they are admitted later (after a week), rapid tests would confirm leptospirosis and appropriate treatment can be given. It is essential that all febrile patients are investigated for leptospirosis, malaria, scrub typhus, viral hepatitis and dengue fever as co-infection can occur. In addition, dialysis (peritoneal dialysis/hemodialysis) and ventilatory support for renal and respiratory failure would definitely decrease mortality.

Chemoprophylaxis

Chemoprophylaxis may be considered for those who are high risk of exposure to potentially contaminated sources (such as farmers, soldiers, rescue teams and those who involved in adventurous sports). Oral doxycycline 200 mg once a day given once weekly throughout period of exposure is the recommended drug for prophylaxis.^{17,36,37}

CONCLUSION

- Utilize modified Faine's criteria for diagnosis of leptospirosis.
- Rapid diagnostic tests are adequate for the diagnosis of leptospirosis.
- Samples may be sent to higher centers with facilities to do MAT, PCR and culture.
- In the first week, diagnosis should be done on the basis of clinical and epidemiological criteria. In the second week, serological diagnostic tests must be done to confirm the diagnosis.
- Empiric therapy should be started for treatment of leptospirosis as soon as clinical diagnosis is made. Do not wait for laboratory test to confirm the diagnosis.
- Oral doxycycline is the treatment of choice for treatment of mild leptospirosis. Injection crystalline penicillin/injection ceftriaxone are adequate to treat severe leptospirosis.
- Co-infection of leptospirosis can occur with malaria, dengue, scrub typhus and viral hepatitis. It is essential to investigate for these diseases even in patients who are confirmed to have leptospirosis.
- Admit patients with severe leptospirosis. Dialysis for acute kidney injury (AKI) and ventilatory support for respiratory failure would definitely reduce mortality.

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