National Guidelines on Management of Leptospirosis

Epidemiology Unit
Ministry of Health, Nutrition and Indigenous Medicine
Sri Lanka
2016
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These national guidelines for management of leptospirosis are published by the Epidemiology Unit, Ministry of Health in 2016.

These guidelines were developed based on the best available evidence at the time of writing.

It is expected to be used in the management of leptospirosis in Sri Lanka. The guideline will be reviewed periodically when new evidence becomes available.

Please forward your comments and suggestions to the following address by post or e-mail.

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Collaborating professional organizations

The guidelines were developed by the Epidemiology Unit in collaboration with the following organizations.

Ceylon College of Physicians
Sri Lanka College of Paediatricians
College of Anaesthesiologists and intensivists of Sri Lanka
Sri Lanka College of Pulmonologists
Sri Lanka Medical Association

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Foreword

Leptospirosis continues to be a disease of public health importance in Sri Lanka with approximately 3,000-5,000 suspected cases reported each year and a Case Fatality Rate (CFR) of 1-2% in the recent past.

Leptospirosis is an illness which has diverse manifestations and complications where the diagnosis and treatment are a challenge. Therefore, having clinical guidelines especially in the Sri Lankan context will be of value to the treating clinician to overcome these challenges.

The Epidemiology Unit with the collaboration of the professional organizations and associations has fulfilled this timely endeavor of developing the management guidelines which would benefit clinicians, serving as a guide to improving diagnosis, notification, investigation and treatment, including the detection and management of complications of leptospirosis.

I hope that this guideline will be utilized by all treating clinicians, thereby improving the management of leptospirosis patients.

I wish to express my sincere gratitude to all who contributed in developing the guidelines.

Dr. P. G. Mahipala
Director General of Health Services
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Sri Lanka.
Preface

Leptospirosis is a zoonotic disease which occurs worldwide. However, it is more common in tropical countries such as Sri Lanka. In Sri Lanka, leptospirosis is reported throughout the year with two peaks generally observed which coincide with paddy cultivation. High humidity and heavy rainfall may cause outbreaks because of widespread exposure to flood water. It is an important public health problem associated with significant morbidity and mortality in Sri Lanka.

The clinical presentation of leptospirosis varies from mild illness to severe life threatening illness. The infection is potentially serious, nevertheless treatable. Therefore, guidelines for management of leptospirosis are needed to ensure uniformity in how the condition is managed.

This National guideline has been developed with the collaboration of the Ceylon College of Physicians, Sri Lanka College of Pediatricians, College of Anesthesiologists of Sri Lanka, Sri Lanka College of Pulmonologists and Sri Lanka Medical Association. The experts who formed the National Guideline Development Committee were clinicians from different specialties, microbiologists and public health specialists. I extend my gratitude to all members of the National Guideline Developing Committee. Further, I would like to acknowledge the support given by all other staff members of our unit who made this a reality. The encouragement given by Dr. P.G. Mahipala (DGHS) and Dr. Sarath Amunugama (DDG-PHS1) is greatly appreciated.

I sincerely hope that these National guidelines will be of help for medical professionals to effectively manage leptospirosis.

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Sri Lanka.
List of Abbreviations

ABG - Arterial Blood Gas
ABST- Antibiotic Susceptibility Test
AKI – Acute Kidney Injury
AKIN- Acute Kidney Injury Network
ALI- Acute Lung Injury
ALT- Alanine Transaminase
APD-Acute peritoneal dialysis
ARDS- Acute Respiratory Distress Syndrome
AST-Aspartate Transaminase
CBS- Capillary Blood Sugar
CFR- Case Fatality Rate
CPK- Creatine phosphokinase
CRP- C-Reactive Protein
CRRT-Continuous renal replacement therapy
CSF- Cerebrospinal fluid
CVP-Central Venous Pressure
DIC-Disseminated intravascular coagulopathy
DNA-Deoxyribonucleic acid
ECG-Electrocardiogram
eGFR-Estimated Glomerular Filtration Rate
ELISA- Enzyme linked immunosorbent assay
EMJH-Ellinghausen-McCullough-Johnson-Harris
ESR-Erythrocyte Sedimentation Rate
FFP-Fresh Frozen Plasma
GCS-Glasgow Coma Scale
HD-haemodialysis
HDU-High Dependency Unit
HRCT-High resolution Computed Tomography
HUS-Hemolytic Uremic Syndrome
ICU- Intensive Care Unit
KDIGO-Kidney Disease: Improving Global Outcome
MAT-Microscopic Agglutination Test
MSD-Medical Supplies Division
MOH-Medical Officer of Health
MRI-Medical Research Institute
NSAIDs-Non Steroidal Anti Inflammatory Drugs
PCR-Polymerase Chain Reaction
PD-Peritoneal dialysis
PDHS-Provisional Director of Health Services
PHI-Public Health Inspector
PT-Prothrombin Time
RDHS-Regional Director of Health Services
RE-Regional Epidemiologist
SBP-Systolic Blood Pressure
TTP-Thrombotic Thrombocytopenic Purpura
UFH- Unfractionated Heparin
UFR-Urine Full Report
1. Introduction

Leptospirosis is a zoonotic illness with a global disease burden impacting both developed and developing nations. It is caused by pathogenic spirochetes of the genus *Leptospira*. The pathogenic *L. interrogans* has more than 250 serovars arranged in 25 serogroups. In Sri Lanka, suspected leptospirosis is a notifiable disease.

The spirochetes colonize the proximal renal tubules of the carriers that include both wild and domestic farm animals, including rodents, cattle, dogs and pigs, and are excreted in urine. Rats and rodents, cattle, dogs and pigs have shown to be some of the reservoir hosts present in Sri Lanka.

Transmission to humans may be direct with inoculation with infected animal tissue or body fluids, or indirect with the organisms entering via mucosal surfaces or damaged skin from infected urine or contaminated environments such as moist soil in agricultural lands, lakes, streams and rivers. Several studies have shown survival of pathogenic leptospires in the environment ranging from 3-14 days.

In 2008, Sri Lanka reported the largest outbreak of leptospirosis with 7423 suspected case notifications and 204 deaths with an incidence rate of 35.7/100,000 population. The CFR was 2.7% and Colombo, Gampaha, Matale, Kurunegala and Kalutara districts were mainly affected.

Sri Lanka, with 28% of its growing population in the agriculture sector, has a reported annual case incidence of 5.4/100,000 population, mostly from the southern and north central regions where the disease is considered hyper-endemic. Also, seropositivity to leptospirosis has been shown in other occupational groups such as workers in coconut plantations and desiccated coconut mills, sugar cane workers, abattoir workers and fish market workers.

An analysis of hospital based sentinel data from 2005 to 2008 showed that the majority of patients are men, aged 30–49 years, who were agricultural workers or labourers, and people who work in paddy fields and marshy/muddy land. However, there are also reports of outbreaks in affluent populations associated with recreational activities such as white water rafting suggesting a wider range of exposure risks.

The exact pathogenic mechanism of leptospirosis is yet to be elucidated, but the wide variation in clinical manifestations points to a diverse range of contributing
factors. The disease is described as biphasic with a bacteraemic phase and an immune phase. In the bacteraemic phase leptospiroa proliferate and disseminate throughout the body causing direct tissue damage. In the immune phase, which is marked by the presence of IgM antibodies in blood, leptospiroa are cleared from most sites of the body but the tissue damage continues due to immune mechanisms.

Leptospirosis can have a markedly varied clinical course. The incubation period is usually 5–14 days, with a range of 2–30 days. Most infections will be asymptomatic or mimic a mild flu and may pass without coming to medical attention. However, a small number of cases can develop the severe form of illness with multi organ failure and a CFR of over 40%.

In the initial bacteraemic phase, there is an acute onset fever with chills and rigors, headache, myalgia, nausea and vomiting. Conjunctival suffusion usually appears in the third day of illness and is characteristic but non-specific. Myalgia is characteristic in the calf but may also be prominent in the back and neck. In the immune phase the fever and other constitutional symptoms may persist in some patients.

The onset of organ involvement will be apparent in severe disease with the development of oliguria, jaundice, meningism, haemorrhage, shock, pulmonary involvement and myocarditis. The most common organ involved is the kidney with an interstitial nephritis and acute tubular necrosis leading to acute kidney injury. Pulmonary involvement and multi-organ involvement has higher CFRs.
References:

2. **Surveillance**

Surveillance is a key strategy in leptospirosis control by generating essential epidemiological information, determining the incidence and distribution of the disease and their implications for effective public health strategies.

The communicable disease surveillance system in Sri Lanka is empowered by the Quarantine and Prevention of Diseases Ordinance enacted in 1897, with subsequent amendments, and identification of leptospirosis as a notifiable disease.

Leptospirosis reporting system has two main components.

I. Routine notification system
II. Sentinel site based special surveillance system

**Routine Notification System**

- **Suspected leptospirosis patient**
- **Medical doctor/ Hospital**
- **MOH**
- **Regional Epidemiologist**
- **Epidemiology Unit**
- **Notification card H544**
- **Range PHI**
- ***Field investigation**
* Field Investigation activities carried out by Public Health Inspector (PHI)

- Obtains relevant information from the patient, medical records and his/her family members
- Verifies the diagnosis
- Ensures that the patient is taking proper treatment
- Encourages continued treatment
- Assesses the health of the contact persons and guides them for necessary treatment if needed
- Observes the environment of the patient to locate potential source of leptospirosis infection
- Health education regarding leptospirosis.
- Takes control measures and ensures prevention of possible outbreaks/spread in the area.
- Reports the findings to Medical Officer of Health (MOH)

Note: Reporting to the Epidemiology Unit and the Regional Epidemiologist (RE) by the MOH is done both paper based and electronically (e-surveillance) as part of the routine notification system.

**Sentinel site based special surveillance**

Sentinel site based special surveillance is carried out for all leptospirosis patients as a field based and an institutional based investigation process.

**Field based special investigation:** The PHI when doing the field investigation for leptospirosis patients should fill the special surveillance form (Annexure 2) in addition to routine H411 form. Completed special surveillance form is then sent to the central level (Epidemiology Unit) through MOH who is responsible for the completeness and accuracy of data provided.

**Institutional based special investigation:** Any hospital having a consultant physician and/or a paediatrician should fill a site special surveillance form for each patient (Annexure 2).

The Infection Control Nursing Officer or an officer designated by the Medical-Officer-In-Charge in these hospitals is tasked with carrying out the investigation while the patient in the ward and the completed special investigation form is sent to the Epidemiology Unit.
Investigation of suspected leptospirosis deaths

All suspected leptospirosis deaths should be investigated and the death investigation form (annexure 3) filled and sent to the Epidemiology Unit. In addition to the death investigation, all deaths need to be reviewed at the hospital. The responsibility of conducting death reviews is with the head of the institution. The Regional Epidemiologist should assist the coordination of the activity.

References:


3. Case definition of leptospirosis

SUSPECTED CASE OF LEPTOSPIROSIS

Acute febrile illness
with at least any one of the following: headache, myalgia, prostration, jaundice, conjunctival suffusion, oliguria, features of meningeal irritation, haemorrhage, features of cardiac failure or arrhythmia, cough, breathlessness, skin rash,

and/or

History of exposure (Table 1)

and/or

Evidence of organ involvement (Table 2)

Suspected leptospirosis is a notifiable disease

Confirmed case: A clinically suspected patient with laboratory confirmed leptospirosis.

Laboratory confirmation of leptospirosis

A Positive culture of pathogenic leptospira
A Positive PCR test for pathogenic Leptospira
A MAT titre of ≥1:320, a four-fold rise or seroconversion from acute and convalescent sera
Table 1: HISTORY OF EXPOSURE FOR LEPTOSPIROSIS

- High risk occupations such as paddy farming, construction work, gem mining, sand mining, working in “keerakotu/kohilakotu”
- Recreational activities in paddy fields/muddy grounds, white water rafting
- Contact with potentially contaminated water such as cleaning drains/wells, bathing and washing in small water streams, rivers and lakes, flood water
- Contact with animals or animal tissues such as cattle, buffalo - animal handlers, veterinarians, butchers, rodent control workers, abattoir workers

Contact with water contaminated with urine from an animal known to be a reservoir species is the most important risk condition in transmission

Known reservoir species include rats and other rodents, buffalo, cattle, dogs and pigs

The presence of breached skin increases the risk of infection

Table 2: EVIDENCE OF ORGAN INVOLVEMENT IN LEPTOSPIROSIS

EVIDENCE OF HEPATIC INVOLVEMENT

The presence of one or more of the following
- Jaundice
- Tender hepatomegaly
- Aspartate Transaminase (AST) or Alanine Transaminase (ALT) increased more than thrice the upper limit of normal
- Raised serum bilirubin, serum alkaline phosphatase or serum gamma-GT

EVIDENCE OF RENAL INVOLVEMENT

The presence of one or more of the following
- Suggestive symptoms, such as reduced urine output, haematuria
- Acute kidney injury (AKI) (Acute Kidney Injury Network (AKIN) stage 1 or above)
  - Rise in serum creatinine ≥ 0.3 mg/dl
  - (≥26.5 µmol/l) above baseline within 48 hours
  - Serum creatinine > 1.5 times the baseline within 48 hours
  - Urine output < 0.5ml/kg/hour for 6 hours
- Haematuria, granular casts, red cell casts in the urinary sediment
**EVIDENCE OF PULMONARY INVOLVEMENT**

The presence of one or more of the following
- Oxygen saturation <94%
- Suggestive symptoms, such as cough, breathlessness, haemoptysis
- Respiratory rate > 30/min (> 60/min in infants, >40/min in 1 – 12 years)
- Crackles and wheezes on auscultation of the lungs
- Lung parenchymal involvement on chest radiograph

**EVIDENCE OF CARDIAC INVOLVEMENT**

The presence of one or more of the following
- Suggestive symptoms and signs, such as shortness of breath, chest pain, palpitations, crackles
- Hypotension
- Electrocardiogram (ECG) abnormalities such as arrhythmias, ST segment/ T wave changes, bundle branch block
- Wall motion abnormalities on echocardiography

**EVIDENCE OF HAEMATOLOGICAL INVOLVEMENT**

The presence of one or more of the following
- Bleeding manifestations
- Platelet count less than 130 x $10^9$/L
- Disseminated intravascular coagulopathy (DIC)
4. Laboratory Diagnosis

In leptospirosis, due to the variability in clinical manifestations, the diagnosis is difficult based on clinical criteria alone. Early detection of the infection will facilitate a more focused approach and could prevent complications. Clinically suspected patients with leptospirosis should not wait for the results of the laboratory tests to start treatment.

Laboratory confirmation is equally important for epidemiological and public health reasons. By determining the infecting serovar the potential reservoir host and the likely source of infection can be identified to guide control strategies.

Introduction to diagnostic methods for leptospirosis

Laboratory diagnosis has two methods: direct evidence includes demonstration of leptospires or its Deoxyribonucleic acid (DNA) or isolation, and indirect evidence is based on detection of specific antibodies to leptospires.

Direct Detection Methods

Isolation of leptospires

Leptospiremia occurs during late incubation to the end of the first week of the acute illness. Therefore, blood and Cerebrospinal fluid (CSF) should be obtained as soon as possible on presentation within the first week, before antibiotics. Isolation of leptospires remains the ‘gold standard’ test available in reference laboratories. Since leptospires are highly infectious organisms, it requires bio safety level–3 facilities to culture. Furthermore, it is time consuming, labour intensive and has low diagnostic yield. But it is the method of choice to identify circulating serovars and useful for antibiotic susceptibility test.

Polymerase Chain Reaction (PCR)

PCR has the advantage of diagnosing early disease especially during the acute leptospiraemic phase (first week of illness) before the appearance of antibodies. The sensitivity and specificity of real-time PCR assays are very high. The new methods will detect the pathogenic leptospires and can be classified in to genomospecies.
**Dark Ground Microscopy**

Dark ground microscopy of body fluids has a very low sensitivity and lacks specificity even in well experienced hands. Approximately $10^4$ leptospires/ml are necessary for one cell per field to be visible by dark ground microscopy. It is not recommended as a confirmatory test.

**Antigen Detection Method**

These assays are not available for human leptospirosis. Presently, they are used only in animal urine.

**Indirect Detection Methods**

Most cases of leptospirosis are diagnosed by serology. Serological methods can be genus specific or serogroup specific.

Antibodies in leptospirosis are detectable by day 6 to 10 of disease and reach a peak within 3 to 4 weeks. The antibody levels gradually recede in few weeks to months, but serovar-specific antibodies remain detectable for several years. In 10% of cases antibodies will not be detected.

**Microscopic Agglutination Test (MAT)**

MAT is considered the ‘serological reference’ method. The MAT antibodies usually appear after 7 days of the illness.

Experience is required to reduce the subjective effects of observer variation in MAT even within laboratories. Moreover, live cultures of all serovars /serogroups required for the test as antigens has to be maintained. Hence, the test is usually available only in reference laboratories.

The MAT using pathogenic serovar is highly specific and sensitive when using acute and convalescent sera. But it is time consuming and hazardous because of the risk of exposure to live antigen. Cross reactions may occur with syphilis, viral hepatitis, human immunodeficiency virus (HIV), relapsing fever, Lyme disease, legionellosis and autoimmune diseases.

In Sri Lanka, this test is available in the Reference Laboratory at Medical Research Institute (MRI) and 12 common locally prevalent serovars are used. A titre of $\geq 1:320$ (cut-off recommended for Sri Lanka by the Reference Laboratory), a four-fold rise in titre or seroconversion from acute and convalescent sera are used to confirm the diagnosis in clinically suspected patients.
Studies conducted in the recent past using common regional pathogenic serovars with patient sera and clinical isolates had shown Pyrogenes, Autumnalis and Icterohamorrhagiae as the most common serogroups present in Sri Lanka.

**Enzyme linked immunosorbent assay (ELISA)**

The IgM ELISA is used as a rapid diagnostic assay for leptospirosis in endemic areas. Many laboratories in Sri Lanka use this test in hospital settings. It is important to ensure that the ELISA assay used has high sensitivity and specificity in the Sri Lankan settings. Hence it is advised to obtain guidance in this regard from the National Reference Laboratory for the diagnosis of leptospirosis, Medical Research Institute.

**Antibiotic Susceptibility Test (ABST)**

ABST is usually not done routinely. Only a few centres in the world have the capability to perform the test as leptospira live cultures and expertise needs to be available.

The Reference Laboratory at Medical Research Institute has commenced testing local strains of clinical isolates by broth dilution assay. The test will be available for the following antibiotics: penicillin, cefotaxime, ceftriaxone, ciprofloxacin, doxycycline and azithromycin.

**Specimen collection**

Appropriate timing for the collection of specimen and transport conditions is crucial for the laboratory to confirm patients suspected of leptospirosis. In addition, providing the clinical history and other information in relation to the disease is important for the laboratory professionals to interpret the results of these tests so as to support the clinicians to arrive at the most appropriate diagnosis.

Table 3 will guide you how and when to collect and transport specimens for the laboratory diagnosis of leptospirosis.
<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Specimen to be collected</th>
<th>Best time for collection</th>
<th>Transport requirements</th>
<th>Turn-around time for results (after receipt of the sample to the laboratory)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture for Leptospira In blood or CSF</td>
<td>Inoculate 2 and 3 drops into two tubes of semi-solid or fluid EMJH medium provided under aseptic condition</td>
<td>Within 7 days of illness Before antibiotics</td>
<td>At room temperature, relatively dark place without direct exposure to sunlight</td>
<td>Immediately informed by telephone when a growth is present. Negative report in 6 weeks</td>
<td>Available only at MRI* Information leaflet is provided with the tubes. Blood for culture should not be requested after the 10th day of illness. Large volume of blood in to culture tubes may inhibit the growth of leptospires</td>
</tr>
<tr>
<td>Antibiotic Susceptibility Test (ABST) for leptospira</td>
<td>Leptospira isolates in EMJH medium</td>
<td>Not applicable</td>
<td>At room temperature, dark place without direct exposure to sunlight</td>
<td>Depends on the number of antibiotics requested</td>
<td>This test is available only at MRI*. Not done routinely.</td>
</tr>
<tr>
<td>Polymerase Chain Reaction (PCR) for Leptospira in blood and CSF</td>
<td>Collection method depends on the PCR assay.</td>
<td>Within 7 days of illness</td>
<td>Temperature should be maintained at +4°C</td>
<td>24-48 hours</td>
<td>Only few laboratories do the test. Inquire before sending the samples.</td>
</tr>
</tbody>
</table>
## SEROLOGICAL ASSAYS

<table>
<thead>
<tr>
<th>Method</th>
<th>Sample Collection</th>
<th>Sample Handling</th>
<th>Result Evaluation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic Agglutination Test (MAT)</td>
<td>5ml of blood or 2ml of serum</td>
<td>After 5th day of illness</td>
<td>Within 48 hours</td>
<td>Serological reference test. Available only at MRI. A negative serological result in the early phase of the disease does not exclude leptospirosis Testing of paired sera is necessary in some patients for confirmation.</td>
</tr>
<tr>
<td></td>
<td>collected into plain sterile bottle</td>
<td>Room temperature or +4°C within 2 days of collection If &gt; 2 days of collection separate the serum and send on ice</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2nd sample maybe required depending on the result of the 1st sample)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzyme linked immunosorbent assay (ELISA)</td>
<td>3-5 ml of blood in sterile plain bottle</td>
<td>After 5th day of illness</td>
<td>Within 48 hours</td>
<td>Only antibody assay is available. ELISA kits should be pre-validated before use on patient samples as leptospira show geographical strain diversity which can result in low specificity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Room temperature</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*National Reference Laboratory for the diagnosis of leptospirosis, Medical Research Institute, Colombo 08
Post-mortem specimens

The post-mortem samples should be collected aseptically and as soon as possible after death. The samples should be sent at 4°C to prevent the autolysis of cells. Serological test cannot be performed on decomposed or haemolysed samples.

References


6. Karunanayake, L., Perera, K.C.R., Rajapakse, S., Handunetti, S., A study to determine the circulating serogroups and the antibiotic susceptibility in human leptospirosis in the Western Province, Sri Lanka (ongoing project)

7. Welikumbura, S., A study to compare genus specific MAT with PCR and culture in clinically suspected cases. MD thesis (MD Medical Microbiology), PGIM 2012
5. Out-patient management

Out-patient management criteria

A suspected case of leptospirosis with **NO** organ involvement and/or significant co-morbidities **COULD BE** managed on an outpatient basis

**Antibiotic therapy**

Doxycycline 100mg 12 hourly for 7 days

**Investigations**

- Full Blood Count (FBC)
- Erythrocyte Sedimentation Rate (ESR)/C-Reactive Protein (CRP)
- Serum creatinine /urea, serum electrolytes
- AST/ALT
- Urine Full Report (UFR)

Table 3 will guide you how and when to collect and transport specimens for the laboratory diagnosis of leptospirosis.

**Monitoring**

Monitor urine output at home (provide a mechanism to measure urine output, such as a marked empty saline bottle)

- Review after 48 hours
- Present to Outdoor Patient Department (OPD) earlier if there is
  - appearance of jaundice
  - reduction in urine output <300mL in 12 hours
  - cough or breathing difficulty
- If no admission is needed at 48 hour review, re-assess in another 48 hours.

Decide on subsequent visits based on clinical features and the presence of fever

**Important:** compliance of the patient in carrying out expected / instructed activities at home including monitoring the urine output, looking for symptoms and signs is crucial if a decision is made to manage a leptospirosis patient on an out-patient basis. If such compliance cannot be guaranteed, it is strongly advised to manage the patient on an in-patient basis.
6. In-Patient management

Admission Criteria
Suspected cases of leptospirosis **WITH** organ involvement and/or significant co-morbidities need admission.

Antibiotic therapy

- The following antibiotics can be given intravenously
  - Penicillin G 1.5 million units 6 hourly
  - Ceftriaxone 1 g daily
  - Cefotaxime 1 g 6 hourly
- Intravenous antibiotic can be stepped down to oral Amoxicillin 500mg 8 hourly when the patient improves
- In mild illness Doxycycline 100mg 12 hourly can be given
- Generally antibiotics are continued for seven days

  All medicine given to paediatric age group should be calculated according to body weight.

Antibiotic therapy in special circumstances

- Reduce the dose of antibiotic according to standard guidelines for renal impairment and hepatic impairment.
- In adults with hypersensitivity to penicillin or cephalosporin, doxycycline could be used.
- Doxycycline should be avoided during pregnancy, breastfeeding, and in children under the age of 12 years.
- In children under the age of 12 years with penicillin or cephalosporin hypersensitivity, Azithromycin 10mg/kg on day 1, followed by 5mg/kg/day on subsequent days, or clarithromycin 15mg/kg/day could be given.
General management in the ward

Patients should be monitored in an acute bed, preferably in High Dependency Unit (HDU), with cardiac monitoring and access to oxygen with minimum of 4 hourly observation of vital signs and urine output. If single organ dysfunction is present, hourly observation is required. The modified early warning score can be used as an alert system.

Investigations

- Full blood count, CRP or ESR, serum creatinine, serum electrolytes, ALT, AST, bilirubin, Prothrombin Time
- Blood picture if DIC is suspected
- ECG
- Chest radiograph

Table 3 will guide you how and when to collect and transport specimens for the laboratory diagnosis of leptospirosis.

Fluid management

Strict monitoring of intake and output is necessary. It is not always necessary to catheterise the patient, but this is advisable if there is AKI.

In patients with normal urine output, fluid therapy should be guided by clinical status of hydration. If hydration appears clinically adequate, the 24 hour intake should be 2 to 2.5 litres in adults. In children, normal maintenance fluid requirement should be given.

In oliguric patients, the intake on a particular day should be equal to the previous days output and estimated insensible loss (approximately 500ml). This should be guided by hydration status, and adjusted accordingly. If the previous day output is not known, the hourly intake should be approximately the previous hour’s output and 25ml, adjusted according to hydration status.
Prevention of electrolyte imbalance

Serum potassium and sodium should be routinely monitored. Low potassium should be corrected intravenously. Hyperkalaemia should be managed according to standard protocols. In severe hepatic or renal dysfunction, calcium and magnesium levels should be monitored and corrected. Salt restriction is appropriate if the patient is clinically overloaded or hypernatraemic.

Diet

If hepatic or renal failure is present, a low protein diet should be given. Food or drink rich in potassium should be avoided if AKI is present.

General pharmacological therapy

All potentially nephrotoxic or hepatotoxic drugs should be stopped. Paracetamol could be used for fever, with caution if hepatic impairment is present. Non-Steroidal Anti Inflammatory Drugs should be avoided as they may increase the risk of analgesic nephropathy.

In patients with diabetes it is advisable to stop oral hypoglycaemic drugs and use insulin for glycaemic control, particularly if the patient is unstable. Insulin infusion is preferred in a critically ill patient.

Determination of severity

There are no validated scoring systems to predict severity of leptospirosis. However, there is evidence that the following are associated with severe disease: older age, chronic alcohol abuse, leukocytosis, low packed cell volume, hyponatraemia and raised hepatic transaminases.
Intensive care management

The decision that a leptospirosis patient needs Intensive Care Unit (ICU) management is vested with the treating clinician. However, the box below gives some indications for intensive care management.

### Indications for intensive care management

Any one or more of the following is an indication for ICU care in adults

- Hemodynamic instability
  - Tachycardia or bradycardia (Pulse rate > 110/min or < 50/min), arrhythmia
  - Hypotension not responding to adequate fluid resuscitation (Systolic Blood Pressure (SBP) < 90 mmHg, Mean Arterial Pressure < 65 mmHg), 20% drop from the baseline
  - Evidence of poor peripheral circulation – capillary refilling time > 2 seconds
- Impaired oxygenation (oxygen saturation < 92%)
- Respiratory Rate > 30/min (< 1 year > 60/min, 1-12 years > 40/min)
- Pulmonary haemorrhages
- Acute Respiratory Distress Syndrome (ARDS)
- Significant spontaneous bleeding
- Reduced consciousness – deteriorating of the consciousness as indicated by the continued change in the Glasgow Coma Scale (GCS) level
- Any other life threatening complications
- Evidence of organ dysfunction
- Severe sepsis
Management in the ICU

Management of leptospirosis patients with critical illness should be based on standard critical care and sepsis management guidelines. Vital organ support for these patients should be instituted according to standard protocols. Aspects of management should be based on the following:

- Routine monitoring of haemodynamic, respiratory and biochemical parameters should be implemented. Invasive monitoring (e.g. Central Venous Pressure (CVP)) should be considered if necessary.
- Targeted fluid management and vasopressor support guided by hemodynamic monitoring.
- Inotropic support aided by haemodynamic monitoring, aimed at achieving a mean arterial blood pressure >65mmHg. Noradrenaline would be the preferred inotrope in shock, with the addition of dobutamine if there is evidence of myocarditis.
- Non-invasive or invasive ventilation depending on the severity of impairment of oxygenation or ventilation.
- Haemodialysis may be required for AKI. Conventional haemodialysis may be used if haemodynamically stable. Continuous renal replacement therapy (CRRT) may be required if hypotensive.
- Electrolytes should be checked at regular intervals (sodium, potassium, calcium, magnesium), and corrected according to standard protocols.
- If significant derangement of coagulation is present, correction should be made according to standard guidelines.
- If liver failure is present, this should be managed according to standard guidelines.
- Nutrition should be optimised.
- Targeted sedation with daily interruption of sedation should be instituted.
- Proton pump inhibitors should be given orally or intravenously as prophylaxis for gastric stress erosions.
- Metabolic derangement should be corrected where possible.
- Adequate glycaemic control should be maintained, according to specific guidelines. The Capillary Blood Sugar (CBS) value should be within the range of 110-180 mg/dl.
• Venous thrombo-embolism prophylaxis should be instituted where possible, taking into consideration the coagulopathy which may be present.
• Prevention of secondary complications is of importance, such as adherence to bundled care for ventilator associated pneumonia, and invasive line associated sepsis.
• While standard antibiotic treatment for leptospirosis should be continued, consideration should be given towards the need for extended antibiotic cover for secondary bacterial/nosocomial infection. If the decision of extending the antibiotic cover for secondary bacterial/nosocomial infection is made, blood must be taken for culture/septic screen before starting antibiotics.

All the above steps should be directed to individualized goals and the adherence to such goals should be continuously monitored.
Complications of Leptospirosis

Renal Complications

Management of acute kidney injury (AKI) in leptospirosis

The incidence of AKI in severe leptospirosis varies from 40%-60%. Mortality in leptospirosis associated AKI is around 22%. Several factors are involved in the pathogenesis of AKI in leptospirosis, including the direct nephrotoxic action of leptospirae, hyperbilirubinemia, rhabdomyolysis and hypovolemia. The major histological findings are acute interstitial nephritis, acute tubular necrosis and vasculitis.

Leptospirosis-induced AKI is usually non-oliguric and hypokalemic. Tubular function defects precede a decline in the glomerular filtration rate, which could explain the high frequency of hypokalemia.

The presence of oliguric AKI with hyperkalaemia portends more severe renal damage and a poorer prognosis. High serum creatinine and potassium levels associated with high creatine phosphokinase (CPK) levels may indicate the presence of significant rhabdomyolysis, which itself worsens the AKI.

The urinary sediment in leptospirosis is non-specific and could contain protein, red cells and granular casts.

All patients admitted to hospital with suspected leptospirosis need to have their serum creatinine, serum electrolytes assessed at least daily. Their urine output should be monitored and they should be catheterized if they are unable to pass urine consciously or if there is doubt whether bladder outflow obstruction is present.

A clinical assessment should be made to detect hypovolaemia as indicated by reduced skin turgor, hypotension and tachycardia. CVP should be measured if possible. If hypovolaemia is present, this should be cautiously corrected with oral fluid or intravenous normal saline, guided by clinical parameters.

It is difficult to diagnose hypovolaemia in the presence of co-existing myocarditis. Presence of basal crepitations together with reduced urine output makes hypovolaemia less likely. CVP measurement will be helpful to differentiate hypovolemia from myocarditis.
It is recommended that the current Kidney Disease: Improving Global Outcome (KDIGO) clinical practice guidelines on the management for AKI be adopted. The modified AKIN classification to stage acute kidney injury is shown below:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5-1.9 times baseline or ≥0.3mg/dL (≥26.5μmol/L) increase</td>
<td>&lt;0.5ml/kg/h for 6-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0-2.9 times baseline</td>
<td>&lt;0.5ml/kg/h for &gt;12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3 times baseline or ≥4.0mg/dL (≥353.6 μmol/L) increase or initiation of renal replacement therapy or in patients &lt;18 years, a decrease in Estimated Glomerular Filtration Rate (eGFR) &lt;35ml/min/1.73m²</td>
<td>&lt;0.3ml/kg/h for &gt;24 hours or anuria</td>
</tr>
</tbody>
</table>

A nephrologist should be involved in the management of AKI whenever possible. Patients with AKI stages 2 and 3 and AKI with other organ failure (cardiac, hepatic or pulmonary) must be transferred to a centre with facilities for haemodialysis.

Polyuric renal failure without fluid overload does not necessarily require dialysis. However the presence of pulmonary involvement with AKI is likely to make dialysis necessary.

The definitive indications for dialysis are uraemic pericarditis and uraemic encephalopathy. It may be difficult to distinguish between the pericarditis of uraemia and pericarditis due to direct effects of leptospirosis. Pericardial rub and significant pericardial effusion are more likely to be the result of uraemic pericarditis.

A pH of <7.2 and a potassium > 6.5mmol/L are also likely to require dialysis even in the presence of polyuria. Oliguria (urine output less than 0.5ml/kg/hour) with low bicarbonate and potassium >5mmol/L is likely to require early dialysis.

In the management of AKI due to leptospirosis, daily short intermittent haemodialysis has been shown to be superior to alternate day haemodialysis or peritoneal dialysis. Each dialysis session should be 2.5-3.0 hours.
In haemodynamically unstable patients, continuous renal replacement therapy is required. In the presence of coagulopathy and/or thrombocytopenia, dialysis should be carried out with minimal dose anticoagulation or no anticoagulation. Dialysis should be bicarbonate based, as acetate based dialysis can make acidosis worse.

Acute peritoneal dialysis (APD) has been used successfully in AKI in leptospirosis. However, blind insertion of a rigid acute peritoneal dialysis catheter in patients who are likely to have a coagulopathy is dangerous. Should peritoneal dialysis be the only option a coiled chronic peritoneal dialysis catheter is preferred as patients can be mobilized and the catheter can be kept as long as required.

Hyperkalaemia should be managed as follows:

If K⁺ 6-6.5 mmol/L with no ECG changes, insulin dextrose followed by ion exchange resin and lactulose will be adequate; monitor potassium at six hourly intervals.

If K⁺ 6-6.5 mmol/L and ECG changes are present, administer the following

- Intravenous 10% calcium gluconate 10ml slowly (over 10 minutes)
- 10U soluble insulin in 50ml 50% dextrose over 10 minutes
- Sodium bicarbonate 300-600ml IV if bicarbonate <20mmol/L
- Nebulization with salbutamol
- Ion exchange resin orally or rectally

Dialysis should be commenced if other indications for dialysis are present, or if hyperkalaemia does not respond to initial therapy.

**AKI-practice points**

All patients admitted with suspected leptospirosis should have;

- urine output monitored
- daily serum creatinine and serum electrolytes measured

Detect and treat hypovolemia

Diagnose and stage AKI based on AKIN classification
Transfer to a centre with HD facility if;

- AKI stage 1 with acidosis (pH <7.2) and hyperkalaemia (>6.5 mmol/L)
- AKI stage 2 and 3
- AKI associated with other organ failure

Indications for dialysis are same as for other AKI

Daily short intermittent haemodialysis (HD) is superior to alternate day HD or Peritoneal Dialysis (PD)

Dialysis should be bicarbonate based rather than acetate based

If PD has to be done, a coiled chronic PD catheter is preferred

Hyperkalaemia is uncommon in leptospirosis; its presence indicates poorer prognosis

Management of hyperkalaemia is the same as for other causes
References

4. Herrmann-Storck, C., Saint Louis, M., Foucand, T., Lamaury, I., Deloumeaux, J., Baranton, G., et al. Severe leptospirosis in hospitalized patients, Guadeloupe. Emerging Infectious Diseases 2010; 16(2): 331-4
Pulmonary complications

Pulmonary manifestations are an important and a serious complication in leptospirosis. It is associated with poor outcome. The incidence of pulmonary involvement varies from 20-70% depending on the criteria used for diagnosis, severity of disease, post-mortem diagnosis and population studied.

In the past decade there has been a global increase in severe pulmonary complications of leptospirosis. Pulmonary involvement is reported to be higher in urban rather than rural populations; this could be due to differing pathogenicity of serovars present in urban vs. rural environments. Pulmonary involvement has a male preponderance and an increased incidence in smokers. Mortality rates of 30-60% have been reported in patients with pulmonary involvement.

Two hypothesis have been proposed regarding the pathogenesis of pulmonary involvement in leptospirosis:

- Direct action of the spirochete and their products of degradation on the membrane of parenchymal cells. This action may first cause functional disorders of these membranes, leading to immune mediated vasculitis. This disruption of the vascular endothelium leads to increased permeability and alveolar bleeding.

- An undefined leptospiral toxin that causes endothelial damage to pulmonary capillaries, leading to increased permeability.

There are two main patterns of pulmonary Involvement:

Pneumonitis with or without pulmonary hemorrhage

Acute Respiratory Distress Syndrome (ARDS) / Acute Lung Injury (ALI)

Risk factors for developing pulmonary complications are:

- Age more than 40 years
- Male sex
- Smoking
- Urban environment
- Mean duration of fever at presentation > 5 days
- Bilirubin >34 µmol /L
- Creatinine > 177 µmol/L
- Platelet count < 100 x 10^9/L
- Specific serovars (e.g., serovar Bataviae)
The clinical manifestations of pulmonary involvement in leptospirosis are:

- Cough
- Breathlessness
- Heamoptysis
- Tachypnoea (respiratory Rate > 30/min, <1 year >60/min, 1-12 years >40/min)
- Auscultation findings of crackles and wheezes

**Investigations**

**Radiographic findings**

Findings depend on the stage and severity of disease. Abnormalities are bi-lateral, non-lobar in distribution and have a marked tendency towards peripheral lung.

There are 3 main radiographic patterns

1) **Small Nodular Lesions**: (snowflake like lesions) seen in 57%.

2) **Large Confluent consolidations**: seen in 16%

3) **Diffuse ill-defined ground glass pattern**: seen in 27%

Serial radiographs show a tendency for the nodular pattern to be followed by confluent consolidations and ground glass densities. The extent of radiological involvement co-relates with the severity of pulmonary involvement.

Pleural effusions are uncommon. Sub-segmental atelectasis is a non-specific finding.

Radiologically, ARDS and cardiogenic pulmonary oedema may be difficult to differentiate.

In ARDS there are bi-lateral predominantly peripheral, somewhat asymmetrical consolidations with air-bronchograms.

Cardiogenic pulmonary oedema is more perihilar in distribution. Kerley B lines and pleural effusions may be seen.

**High resolution CT (HRCT) findings**

HRCT may show ground-glass opacities involving all lobes, (predominantly peripheral lung with dorsal distribution.) Consolidations and air space nodules may be seen.
Arterial Blood Gas (ABG) is of use in determining the degree of lung injury. A PaO2/FiO2 ratio ≤ 300 mmHg indicates acute lung injury, and a PaO2/FiO2 ratio ≤ 200 mmHg indicates ARDS.

In patients with pulmonary involvement, continuous pulse oxymetry should be commenced, with serial ABGs to monitor progress. Daily chest radiographs maybe required.

**Treatment of Pulmonary Complications**
The presence of chest radiographic changes is an indication for intensive care.

Some studies have shown that bolus methylprednisolone given within the first 12 hours of the onset of respiratory symptoms may improve the prognosis and reduce or delay the need for mechanical ventilation in pulmonary leptospirosis. Methylprednisolone is given at a dose of 1 gram IV daily for 3 days, followed by oral prednisolone 1mg/kg/day for 7 days. The strength of this evidence is low.

Mechanical ventilation is indicated for patients with severe lung involvement. The following are indications for mechanical ventilation.

- ARDS – PaO2 / FiO2 ≤ 200 mmHg
- Bi-Lateral infiltrates on chest radiography

Mechanical ventilation should follow the standard protocols suggested in the sepsis guidelines (i.e., low tidal volume, lung protective ventilation).

<table>
<thead>
<tr>
<th>Pulmonary complications-practice points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough, breathlessness, haemoptysis, tachypnoea, crackles and wheezes indicate pulmonary complications</td>
</tr>
<tr>
<td>Continuous pulse-oxymetry, daily chest radiographs and daily ABG are indicated</td>
</tr>
<tr>
<td>Development of chest radiograph changes is an indication for ICU care</td>
</tr>
<tr>
<td>In leptospirosis pleural effusions are not a common finding. Therefore if elicited consider other possibilities. (e.g. Dengue Haemorrhagic Fever)</td>
</tr>
<tr>
<td>ARDS due to leptospirosis and cardiogenic pulmonary oedema may be difficult to differentiate</td>
</tr>
</tbody>
</table>
Indications for mechanical ventilation are

- PaO2 / FiO2 ≤ 200 mmHg
- Bi-Lateral infiltrates on chest radiography

Early administration of Intravenous methylprednisolone may improve the prognosis

References


Cardiac Complications

Early reports on leptospirosis indicate that about 10% of patients have cardiac involvement. However, postmortem studies have shown histological evidence of cardiac involvement in the form of myocardial inflammation and vasculitis in as many as 70%. Recent studies using echocardiograms and ECG show that nearly 50 percent of patients have cardiac involvement. The presence of cardiac involvement demonstrated echocardiographically or clinically tends to predict a poor outcome in leptospirosis.

Rhythm abnormality is a common finding in patients with leptospirosis. It is postulated that electrolyte imbalance as well as direct myocardial inflammation is the cause of ECG abnormalities. Relative bradycardia, atrial fibrillation, atrial flutter and ventricular premature beats are the common arrhythmias. Conduction blocks, T wave and ST segment changes are also frequently seen. ECG changes have been shown to return to normal after antibiotic therapy.

Pericarditis, as evidenced by the presence of a pericardial rub, ECG changes and echocardiographic changes, can be seen in leptospirosis. In patients with severe renal dysfunction pericardial involvement may occur due to uraemic pericarditis.

Myocardial dysfunction seen on echocardiography is not common in leptospirosis and cardiac failure is rare. Chest x-ray findings that suggest cardiac failure may be misleading in leptospirosis. Cardiomegaly can be due to pericardial effusion. Non-cardiogenic pulmonary oedema, hemorrhagic pneumonitis and fluid overload can be misdiagnosed as cardiac failure. The value of cardiac biomarkers in diagnosis of cardiac involvement in leptospirosis is unknown.

No specific therapies are available to prevent or treat cardiac involvement in leptospirosis; current management is based on correction of deranged homeostasis and supportive therapy.
Hepatic complications

The classical triad of severe leptospirosis described by Weil in 1886 consisted of fever, jaundice and splenomegaly. Currently Weil’s disease is used to describe severe leptospirosis with hepatic involvement and acute kidney injury. Hepatic involvement is one of the commonest manifestations of severe leptospirosis, and is seen universally when multi-organ dysfunction is present.

Congested sinusoids and distension of the space of Disse have been observed in fatal cases of leptospirosis. Preferential leptospiral attachment to hepatocytes and invasion of the peri-junctional region between hepatocytes has been observed in post-mortem studies, suggesting that direct hepatic damage is caused by leptospira.

The usual clinical manifestations of hepatic involvement are deep jaundice and hepatomegaly. Investigations show a cholestatic picture with elevated direct bilirubin. There is only moderate elevation of hepatic transaminases. Minor elevation of alkaline phosphatase can be seen. Prolongation of prothrombin time is not common. Rarely, elevated indirect bilirubin can be seen in association with haemolysis. Massive hepatic necrosis with acute liver failure is uncommon in leptospirosis. After recovery, transaminases quickly return to normal. However, it may take several weeks for normalization of bilirubin. Recovery is complete with no

Cardiac complications-practice points

Rhythm abnormalities, pericarditis and myocarditis can complicate leptospirosis

Cardiac failure due to myocardial dysfunction is rare

Radiographic changes suggestive of cardiac failure can be misleading; they may be due to other causes such as pneumonitis, fluid overload and ARDS

Cardiac biomarkers are not helpful to diagnose cardiac involvement

There is no specific therapy for cardiac involvement

Current management is supportive therapy and correction of deranged homeostasis
long term sequelae. Isolated liver involvement is not a common cause of death in leptospirosis, and severe liver damage with hepatic failure only occurs together with other organ dysfunction.

There is no specific management for liver involvement in leptospirosis. Hyperbilirubinemia with moderate elevation of hepatic transaminases does not need any treatment; monitoring liver functions for early detection of rare massive hepatic necrosis is sufficient.

Management of acute liver failure in leptospirosis is complicated as it is almost always associated with failure of other organs; especially kidney and heart. Patients should be managed in the intensive care unit. Special attention should be given to coma care, fluid management, haemodynamics and metabolic parameters. Fluid replacement can be difficult due to co-existing oliguria due to acute kidney injury. Comatose patients should be electively intubated to facilitate general care and prevent aspiration pneumonia.

There is evidence that intravenous N-acetylcysteine is effective in early stages of acute liver failure due to a variety of causes. Although there is no evidence relating to the use of N-acetylcysteine in liver failure due to leptospirosis, it could be used based on clinical judgement.

<table>
<thead>
<tr>
<th>Hepatic complications- practice points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical- deep jaundice and hepatomegaly</td>
</tr>
<tr>
<td>Investigations- Elevated direct bilirubin with moderate elevation of transaminases</td>
</tr>
<tr>
<td>Recovery is complete with no long term sequelae</td>
</tr>
<tr>
<td>Usually does not need any treatment</td>
</tr>
<tr>
<td>Massive hepatic necrosis with acute liver failure is uncommon</td>
</tr>
<tr>
<td>N-acetylcysteine can be used in acute liver failure</td>
</tr>
</tbody>
</table>

Haematological complications

Bleeding manifestations are not uncommon in leptospirosis, and are seen often in cases that are fatal. The commonest site of fatal haemorrhage is the lung. Other bleeding manifestations include: haematuria, haematemesis, melaena, epistaxis, petechiae, ecchymosis, bleeding from venipuncture sites etc. The bleeding tendency in leptospirosis is thought to be the result of an imbalance in the equilibrium in haemostasis, the cause of which is yet unknown. This imbalance may lead to disseminated intravascular coagulopathy (DIC).

Activation of the coagulation cascade in leptospirosis patients may lead to a wide spectrum of effects ranging from insignificant abnormalities in laboratory markers to severe thrombo-haemorrhagic syndromes such as DIC, Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP).

Thrombocytopenia is a common finding in patients with leptospirosis, but does not appear to correlate directly with a higher incidence of haemorrhage.

There is no single laboratory test that can diagnose DIC in leptospirosis. Thus, it is of utmost importance to assess the whole clinical picture and laboratory results.

Transfusion of platelets or plasma components in patients with DIC should not primarily be based on laboratory results and should be reserved for patients with bleeding. In patients with DIC and bleeding and a platelet count of <50x10^9/l, transfusion of platelets should be considered. In non-bleeding patients with DIC, prophylactic platelet transfusion should not be given unless there is a high risk of bleeding, or for those undergoing surgery or invasive procedures. The suggested initial dose of platelets is one adult dose (4-6 units of platelets).

In bleeding patients with DIC with prolonged PT and APTT (PTR and APTR >1.5) administration of Fresh Frozen Plasma (FFP) may be useful. There is no evidence that infusion of plasma stimulates the ongoing activation of coagulation. Initial doses of 15 ml/kg of FFP are suggested.

If transfusion of FFP is not possible in patients with bleeding because of fluid overload, consider using factor concentrates such as prothrombin complex concentrate, recognizing that these will only partially correct the defect because they contain only selected factors, whereas in DIC there is a global deficiency of coagulation factors.
Severe hypofibrinogenaemia (<1 g/l) that persists despite FFP replacement may be treated with fibrinogen concentrate or cryoprecipitate. Specific deficiencies in fibrinogen can be corrected by administration of purified fibrinogen concentrates or cryoprecipitate. A dose of 3 g would be expected to raise plasma fibrinogen by around 1 g/l. This can be given as approximately four units of FFP, two cryoprecipitate pools (10 donor units) or as 3 g of a fibrinogen concentrate.

Transfusion of packed cells should be considered at a threshold of 7 g/dL or below, with a target Hb range of 7–9 g/dl, which is standard for all critically ill patients, unless there are specific co-morbidities or acute illness.

There is no place for the use of anti-fibrinolytic agents in patients with DIC.

In cases of DIC where thrombosis predominates, such as arterial or venous thromboembolism, severe purpura fulminans associated with acral ischaemia or vascular skin infarction, therapeutic doses of heparin should be considered. In patients where there is a co-existing high risk of bleeding there may be a benefit of using a continuous infusion of Unfractionated Heparin (UFH) due to its short half-life and reversibility. Weight adjusted doses (e.g. 10 U/kg/h) may be used without prolonging the APTT ratio to 1.5–2.5 times the control. Monitoring the APTT in these cases may be difficult and clinical observation for signs of bleeding is important.

In critically ill, non-bleeding patients with DIC, prophylaxis for venous thromboembolism with prophylactic doses of heparin or low molecular weight heparin is recommended.

<table>
<thead>
<tr>
<th>Haematological complications- Practice points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia does not correlate with higher incidence of bleeding</td>
</tr>
<tr>
<td>Coagulation abnormalities can vary from minor laboratory abnormalities to severe thrombo-haemorrhagic syndromes</td>
</tr>
<tr>
<td>Indication for platelet transfusion -DIC and bleeding with platelet &lt;50 x 10^9/L</td>
</tr>
<tr>
<td>Indication for FFP- DIC and bleeding with APTR &gt;1.5</td>
</tr>
<tr>
<td>Indication for packed cell transfusion- Hb &lt; 7 g/dL</td>
</tr>
</tbody>
</table>
References


Annexure I: Prophylaxis

- Pre-exposure chemo prophylaxis is only recommended for well recognized high risk groups, and is not advocated as a routine or leading preventive measure.

- If a decision to give chemoprophylaxis is made by the public health authorities, it should be closely monitored by the MOH and the field public health staff. The PHI could be involved in the issuance of medicine. A register should be maintained containing all the names, addresses and occupation of recipients and arrangements should be made to regularly distribute drugs to them for the required period.

- Doxycycline 200 mg once a week is the recommended dose for prophylaxis. This should be started few days (within one week) prior to the exposure and continued throughout the period of exposure.

- It is the responsibility of the relevant MOH to identify the risk period, in consultation with the Regional Epidemiologist and/or Epidemiology Unit where required

- The relevant MOOH should strengthen the disease surveillance activities in their areas, especially where prophylaxis is provided. MOOH who wish to provide prophylaxis should send the drug estimate through relevant RE, Regional Director of Health Services (RDHS) and Provisional Director of Health Services (PDHS) to the Medical Supplies Division (MSD) with a copy to the Chief Epidemiologist

- Doxycycline can be taken with or without food, preferably with a full glass of water. It is contraindicated in,
  
  - Age <12 years
  - Pregnancy
  - Lactating mothers
  - The presence of previous allergy

- Doxycycline is generally not prescribed to patients with significant liver or kidney disease. In case of any doubt, advice may be sought from a consultant physician in the nearest hospital.
Annexure 2: Site special surveillance form

**CASE INVESTIGATION FORM**

**EPIDEMIOLOGY UNIT, MINISTRY OF HEALTH**

The Public Health Inspector should investigate and complete this form. Medical Officer of Health is responsible for the completeness and accuracy of data provided. Necessary data should be obtained from the patient, his/her relatives and from the diagnostic card. Early investigation and return are essential.

<table>
<thead>
<tr>
<th>Week Ending of notification</th>
<th>d</th>
<th>m</th>
<th>y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Please write the Serial No given in the Infectious Disease Register (ID Register) in the MOH office</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### A. PARTICULARS OF PATIENT (Please (✓) appropriate box where applicable)

1. Name of patient (BLOCK LETTERS)
2. Residential Address
3. Age y m m
4. Date of Birth y y / m m (dd/mm/yyyy)
5. Sex
   - 1. Male
   - 2. Female
   - 3. Unknown
6. Ethnic group
   - 1. Sinhalese
   - 2. Tamil
   - 3. Moor
   - 4. Others
   - 5. Unknown
7. Occupation
8. DPCHS Division
9. MOH area

### B. PRESENT ILLNESS/OUTCOME

10. Date of onset of symptoms: y m m
11. Where did the patient first seek medical advice?
   - 1. Government hospital
   - 2. Private hospital
   - 3. Private practitioner
   - 4. Ayurvedic institution (public/private)
   - 5. Other (specify)
12. Was patient admitted to hospital?
   - 1. Yes
   - 2. No
   - 3. Not known
   - To Q.22
13. If yes, date of admission y m m
14. Name of hospital
15. Ward
16. BHT No.
17. Was patient transferred from some other hospital?
   - 1. Yes
   - 2. No
18. If Yes from where the patient was transferred?
19. BHT No. of transferring hospital
20. Outcome of the case
   - 1. Cured
   - 2. Died
   - 3. Not known
   - 4. Transferred to (specify): Hospital
21. Date of discharge/transfer or death y m m

### C. CLINICAL DATA

Case definition: acute febrile illness with headache, myalgia and prostration associated with any of the following: conjunctival suffusion, meningal irritation, anuria/oliguria/proteinuria, jaundice, haemorrhage, cardiac arrhythmia/failure, skin rash AND history of exposure to infected animal/contaminated environment AND laboratory isolation of pathogenic leptospirosis/positive serology (MAT)

22. Symptoms and complications: If available, refer to patient's notes/diagnosis card before completing this section
   - 1. Acute fever (Sudden onset of fever)
   - 2. Headache
   - 3. Myalgia (severe muscle pain)
   - 4. Prostration (Severe tiredness or lack of energy)
   - 5. Jaundice (Yellowish discoloration of skin or eyes)
   - 6. Conjunctival suffusion (Redness of eyes)
   - 7. Meningal irritation
   - 8. Anuria/oliguria (No urine output or reduced urine output)
   - 9. Haemorrhage (Bleeding from unusual sites. E.g.: gum bleeding, bleeding from rectum, vomiting of blood, blood stained urine, bleeding under the skin etc.)
   - 10. Cardiac failure/arrhythmia
   - 11. Skin rash
   - 12. Cough
   - 13. Haemoptysis
   - 14. Breathlessness
   - 15. Other (specify)...

For office use only

Compatible with the case definition: 1. Yes 2. No
D. LABORATORY DIAGNOSIS


24. If yes, 

<table>
<thead>
<tr>
<th>Test</th>
<th>Blood</th>
<th>Urine</th>
<th>Other body fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>Non</td>
<td>Known / NA</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>Non</td>
<td>Known / NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Known / NA</td>
</tr>
</tbody>
</table>


26. If yes, 

<table>
<thead>
<tr>
<th>Investigation – MAT*</th>
<th>1st specimen</th>
<th>2nd specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data of collection of specimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory (MWH/ Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>govt/Private/ Not known)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results (Mark NA if test results are not available and PP if pending)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MAT = Microscopic Agglutination Test

E. INFORMATION ON DISEASE TRANSMISSION

27. Other laboratory investigation results:

F. PROPHYLAXIS

28. Possible source of contamination:

☐ 1. Paddy field
☐ 2. Other agricultural land (sugar cane, chena)
☐ 3. Marshy/muddy land
☐ 4. Other water related source (sewer, irrigation, fisheries)
☐ 5. Animal husbandry, veterinary
☐ 6. Other (specify): ____________________________________________

29. Grama Sevaka Division where the likely sources of contamination is/are located:

I. __________________________________________________________
II. _________________________________________________________
III. _________________________________________________________
IV. _________________________________________________________


31. Did any of the patient's family members, companions, associates or neighbours develop a similar illness (within a one month period) with acute fever, headache, myalgia, prostration and any other signs mentioned under question 21? □ 1. Yes □ 2. No □ 3. Not known

32. Was the patient on chemoprophylactic treatment for leptospirosis at the time of onset of illness? □ 1. Yes □ 2. No □ 3. Not known

33. If yes, How many weekly doses have been taken before onset of illness? □□


35. Remarks:

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

Signature: ____________________ Name: ________________________________
Date: ________________________ Designation: ___________________________

Please return to:
Epidemiologist, Epidemiology Unit, 231, De Saram Place, Colombo 10
email: ohepid@citnet.lk Tel: 011-2886112 / 2886548 Fax: 011-2886583

40
Annexure 3: Death Investigation Form

REPORT ON DEATH DUE TO LEPTOSPIROSIS

INSTITUTIONAL DEATH REVIEW

To be completed by the Specialist or the Senior Medical Officer who attended the patient

Name of the hospital: .................................................................................................................................

Ward No: .......................................................... BHT No: ..................................................................................

Part I: Basic Information of the Patient

1) Name: ...........................................................................................................................................

2) Age: .......................................................... 3) Sex: ..................................................................................

4) Address: ...........................................................................................................................................

5) RDHS Area: .......................................................... 6) MOH Area: ..........................................................

Part II: Admission details

7) Date and time of admission to the hospital YY MM DD Time

8) Whether transferred? Yes □ No □

9) If yes, from which hospital? ..............................................................................................................

10) Whether the BHT stamped ‘urgent’? Yes □ No □

11) Place of admission: Ward □ ETU □

12) Time of admission to ward/ETU: ......................................................................................................

13) Time of examination by the Medical Officer: ...................................................................................

Part II: History

14) Date of onset of symptoms YY MM DD

15) Where did the patient first seek medical advice?

Government Hospital □ Private Hospital □

General Practitioner □ Others (Specify) □

Name: ..................................................................................................................
16) Was patient admitted to a hospital after he first sought advice? ........................................

17) Date of first hospital admission: Y Y M M D D

18) History of any chronic diseases: ...........................................................................................

Part IV: Details of clinical examination

19) On admission, did the patient have any symptoms/signs suggestive of hepatic and/or renal impairment, cardiac failure and/or meningeal irritation?  Yes ☐ No ☐

If 'yes', provide details:

......................................................................................................................................................

......................................................................................................................................................

20) At the time of death, did the patient have any symptoms/signs suggestive of hepatic and/or renal impairment, cardiac failure and/or meningeal irritation?  Yes ☐ No ☐

If 'yes', provide details:

......................................................................................................................................................

......................................................................................................................................................

Part V: Details of clinical management

21) Briefly give the details of medical treatment given: .................................................................

......................................................................................................................................................

......................................................................................................................................................

22) Comments on other aspects of management

<table>
<thead>
<tr>
<th>Maintenance of</th>
<th>Satisfactory</th>
<th>Unsatisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid balance chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chart of vital signs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Part VI: Details of laboratory investigation

23) Please furnish the results of following investigations (if available):

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Date &amp; Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td></td>
</tr>
<tr>
<td>Urine full report / proteinuria</td>
<td></td>
</tr>
<tr>
<td>Blood Urea / creatinine</td>
<td></td>
</tr>
<tr>
<td>SGPT / SGOT</td>
<td></td>
</tr>
<tr>
<td>Direct microscopy</td>
<td></td>
</tr>
<tr>
<td>SGPT / SGOT</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
</tr>
<tr>
<td>MAT (Serology) (1st &amp; 2nd)</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td></td>
</tr>
<tr>
<td>Any other</td>
<td></td>
</tr>
</tbody>
</table>

Part VII: Cause of death

24) Date and time of death:  
   YY MM DD  Time:  

25) Probable cause of death:  

26) Co-morbidity conditions that might have contributed:  

27) Autopsy findings:  

28) Brief statement of events leading to death:  


29) View of the Specialist Medical Office on factors contributing to the death (This question should only be answered by the Specialist Medical Officer in-Charge of the particular unit)

Mark (V) where relevant.

<table>
<thead>
<tr>
<th>Delay in seeking treatment by the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in transferring patient (if it was a transferred case)</td>
</tr>
<tr>
<td>Lack of or non-availability of services (laboratory, transfusion etc.)</td>
</tr>
<tr>
<td>Shortcomings in the clinical management (delayed diagnosis etc.)</td>
</tr>
<tr>
<td>Any other factors identified (specify)</td>
</tr>
</tbody>
</table>

30) List the actions already taken / proposed to be taken to overcome the deficiencies identified:

________________________________________________________________________________________________________________________________________________
________________________________________________________________________________________________________________________________________________
________________________________________________________________________________________________________________________________________________

Name / Designation: ........................................................................................................
Signature: ........................................................................................................ Date: ................

Observations of the head of institution:
________________________________________________________________________________________________________________________________________________
________________________________________________________________________________________________________________________________________________
________________________________________________________________________________________________________________________________________________

(Signature)

Date: ........................................
Name: ........................................
Designation: ........................................
Institution: ........................................

Please fill this form and send to

Chief Epidemiologist
Epidemiology Unit
231, De Saram Place, Colombo 10
Telephone: 011 2695112, 011 2681548 Fax: 011 2696583

A photo copy of the form to be kept in the institution