Clinical Guidelines

for Diagnosis and Management of Leptospirosis

2016

Ministry of Health and Medical Services

Republic of Fiji

MINISTRY of HEALTH & MEDICAL SERVICES

Shaping Fiji's Health

Preface

Leptospirosis is a priority outbreak-prone diseases for the Fiji Ministry of Health and Medical Services (MHMS). Endemic disease is responsible for substantial morbidity and mortality, and large outbreaks have occurred, including two severe post-flooding outbreaks in 2012 with 576 reported cases and 40 deaths. Inaccurate diagnosis, inconsistent clinical management and delays in referral are likely to be responsible for progression from mild treatable disease to severe complications and deaths. High quality clinical management can reduce disease burden and mortality, and accurate reporting will improve public health surveillance and response. In this context, the Fiji MHMS requested WHO support to develop national guidelines for clinical diagnosis and management of leptospirosis. The guidelines aim to improve patient outcomes by standardising and optimising clinical assessment, diagnosis, management, referral, and reporting of leptospirosis cases. Recommendations are based on current scientific evidence and access to medical care and laboratory services in Fiji.

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The guidelines were developed after consultations with the following **clinicians and public health practitioners at Fiji Ministry of Health and Medical Services, WHO Division of Pacific Technical Support (Suva), Colonial War Memorial Hospital, and Fiji National University** (in alphabetical order):

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This guideline should be reviewed every 5 years, or earlier if there are significant changes in the availability of diagnostic tests or access to health care.

CONTENTS:

1. INTRODUCTION

Leptospirosis is one of the most common zoonotic diseases in the world with an estimated 1 million cases annually, and particularly high risk in tropical regions including the Pacific Islands. Infection is caused by pathogenic leptospires that are excreted in the urine of infected animals, including rodents, domestic pets, livestock and wildlife. Leptospires can survive in soil or water for weeks or longer, and humans can become infected through direct contact with infected animals, or through contact with soil or water contaminated by the urine of infected animals. Risk factors for human infections and drivers of outbreaks depend on interactions between humans, animals, and the environment. Environmental factors play an important role in disease transmission, and an increased risk of leptospirosis has been linked to high rainfall, flooding, natural disasters, poor sanitation, and population growth and urbanisation in developing countries, particularly in urban slums [1,2]. Human activities that increase exposure to animals, soil, mud and water are also important risk factors.

In the **Pacific Islands**, important risk factors include the tropical climate, high rainfall, flooding, and close contact with livestock. Many people also live a very outdoor lifestyle with close connection with the environment, e.g. swimming, bathing, and washing in the rivers, walking barefoot, and gardening [3-9].

In **Fiji**, clinical and epidemiological studies have identified males, iTaukei, and young adults aged 20-49 years as high-risk groups [10-12], most likely related to greater occupational and recreational exposure to animals, soil, mud and water. Other risk factors include living in rural areas or villages; poverty, including the lack of government water supply at home; farming, working outdoors or in abattoirs; touching rats or mongoose; raising pigs at home or the presence of pigs in the community; exposure to flood waters; and living close to rivers or in areas of high rainfall [12]. The number of cases peak in the wettest months from February to May.

In 2012, two large outbreaks occurred after severe flooding with 576 reported cases and 40 deaths [12]. In comparison, previous studies in Fiji reported 487 cases during a 13-year period from 1969-1981 [10], and 576 cases during an 8-year period from 2000-2007 [11]. **Figure 1** shows the number of *Leptospira* ELISA IgM positive cases reported from 2010 to week 39 of 2015 by gender and division. Of cases where gender was recorded, the male:female ratio was 1.6.

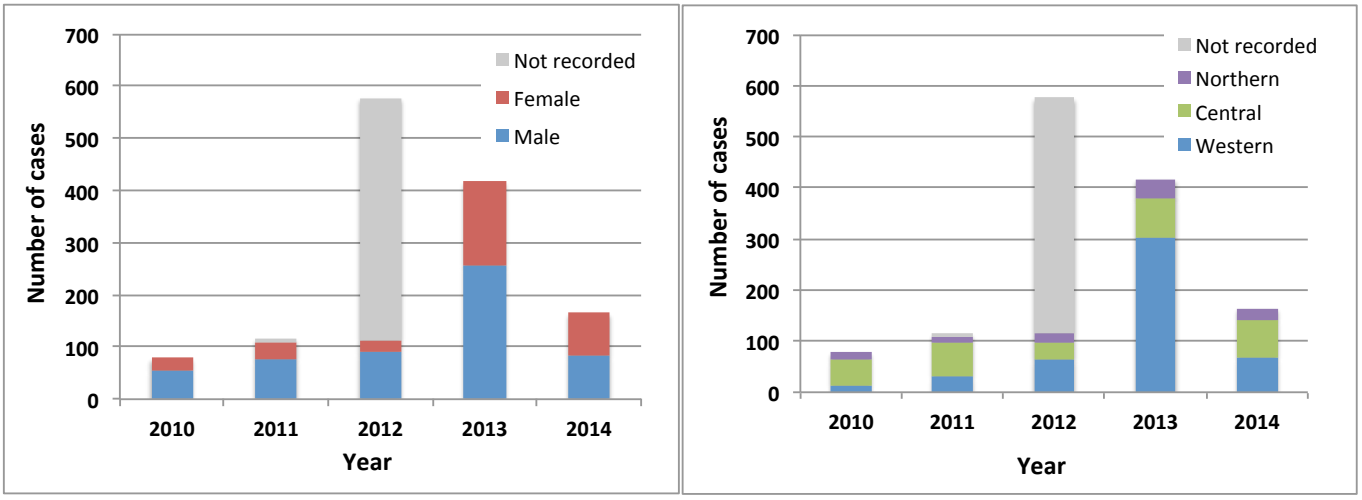

Figure 1. *Leptospira* ELISA IgM positive cases reported in Fiji from 2010 to 2014, stratified by gender and Division of residence. Note that gender and Division were not recorded in a large number of cases in 2012. Data provided by Fiji Ministry of Health & Medical Services.

Important risk factors for leptospirosis Fiji include:

- Demographics: male, iTaukei, young adults
- Occupational risk: farmers (livestock, cane, taro, other crops), abattoir workers, outdoor workers, cleaning streams, exposure to sewage and garbage
- Contact with animals: livestock (especially raising pigs), rodents, pets, wildlife
- Contact with freshwater, soil, or mud: floodwaters, rivers, lakes, waterfalls
- Household environment: live in rural area or village, no metered water at home
- Live or work in areas with high risk of leptospirosis (e.g. recent outbreaks)
- Epidemiological link to another case (e.g. household member or co-worker)

Patients with multiple risk factors are at even greater risk of infection. A recent epidemiological study of leptospirosis in Fiji showed that the combination of multiple independent factors could significantly increase the risk of infection [12]. **Figure 2** shows a seroprevalence estimation chart for leptospirosis in Fiji based on gender, ethnicity, community type, availability of metered water at home, and work location. It is important to note that the numbers reported in the chart are the percentages of people who had antibodies to leptospirosis (i.e. infected in recent years), but not all infected persons develop symptomatic illness. Figure 2 works on the same concept as cardiovascular risk prediction charts.

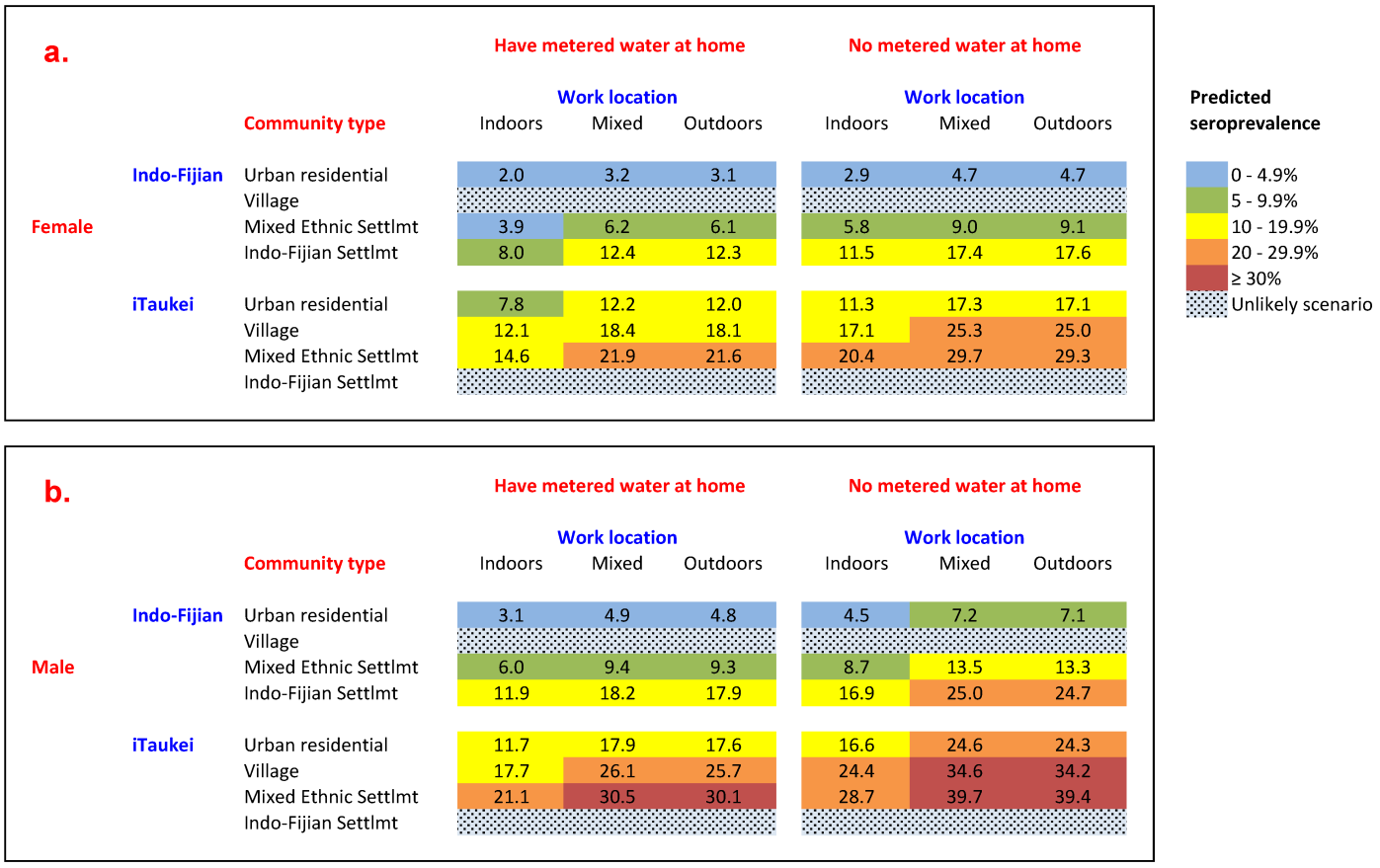

Figure 2. Seroprevalence estimation chart showing the combined effects of independent risk factors on the estimated seroprevalence of leptospirosis infection in a) females, and b) males [12]. Seroprevalence was defined as the percentage of study participants with reactive microscopic agglutination test (titre ≥ 1:50) to at least one *Leptospira* serovar.

A recently published paper provides detailed information on the epidemiology of human leptospirosis in Fiji, including environmental factors for disease transmission:

Lau CL, Watson CH, Lowry JH, David MC, Craig SB, Wynwood SJ, et al. (2016) ***Human Leptospirosis Infection in Fiji: An Eco-epidemiological Approach to Identifying Risk Factors and Environmental Drivers for Transmission.*** *PLoS Negl Trop Dis 10(1): e0004405.* Link: http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004405

Leptospirosis is a significant public health problem in Fiji and the Pacific Islands. Although many infections are mild or asymptomatic, severe complications can result in significant morbidity and mortality, as well as socioeconomic losses related to health care costs, loss of working days, and reduced productivity. Early diagnosis and treatment can reduce the risk of severe complications [13], and this document aims to provide guidelines for clinical best practice to reduce leptospirosis-related morbidity and mortality in Fiji. Accurate case notification by clinicians is also crucial for disease surveillance, which helps to inform public health response as well as improve understanding of the epidemiology of leptospirosis in Fiji.

2. OVERVIEW OF APPROACH TO MANAGEMENT OF SUSPECTED LEPTOSPIROSIS

In Fiji, ***diagnosis and management of leptospirosis should be based primarily on clinical assessment*** – a detailed history and a thorough clinical examination is therefore crucial. For all patients who fit the case definition of suspected leptospirosis, the following steps should be followed. An overview of the approach is included as a summary page in **Appendix A**. Detailed descriptions of each step are explained in different sections of this document, and summarised in wall charts – **Appendix B** for outpatient management, **Appendix C** for inpatient management, and **Appendix D** for ICU and ED.

Step 1. Clinical assessment: history, examination, risk factors, and differential diagnoses.

Step 2. Does the patient fit the case definition for suspected leptospirosis? If yes:

Step 3. Determine initial level of care required based on clinical assessment.

Step 4. Commence treatment and arrange referral if indicated.

Step 5. Order investigations if laboratory available:
a) General investigations – FBC, UEC, LFT, CPK, CXR, ECG, urinalysis, and others as indicated
b) Leptospirosis diagnostic tests if available:
- Rapid Diagnostic Test (RDT)
- *Leptospira* ELISA IgM
- PCR (molecular diagnosis)

Step 6. Classify cases as suspected, probable, or confirmed based on results of leptospirosis diagnostic tests

Step 7. Notify all cases and deaths to public health. Cases should be notified as ***suspected***, ***probable***, or ***confirmed*** using case definitions.

Step 8. Initiate case investigation or outbreak investigation if indicated.

3. CLINICAL ASSESSMENT

3.1. HISTORY and EXAMINATION

Clinical manifestations of leptospirosis are highly variable and often difficult to distinguish from other causes of acute febrile illnesses. After an incubation period of 5 to 14 days (range 1 to 30 days), leptospirosis causes a biphasic illness with an early bacteraemic phase lasting 7 to 10 days, followed by a late phase associated with immunologically mediated organ damage, severe complications and high mortality rates. Clinical presentations range from mild non-specific febrile illnesses to severe life threatening complications including acute renal failure, pulmonary haemorrhage, cardiac arrhythmias, shock, liver failure, coagulopathy, and aseptic meningitis. Weil's disease is the classic triad of jaundice, renal failure, and haemorrhage in the late phase of severe leptospirosis, but the three manifestations do not always occur together, and the term Weil's disease is often used loosely refer to severe leptospirosis.

Diagnosis of leptospirosis in Fiji should be primarily based on CLINICAL ASSESSMENT.

Patients who fit the case definition for SUSPECTED LEPTOSPIROSIS should be promptly treated so that the risk of severe complications and death are minimised. The case definition for suspected leptospirosis (Section 4) is based entirely on clinical assessment – a detailed history and thorough examination is therefore crucial for early diagnosis.

ONSET OF ILLNESS: The number of days since the onset of symptoms is important for determining which laboratory tests should be ordered, and for interpreting test results. The date of onset of illness should also be recorded on laboratory request forms and notification forms.

EARLY PHASE: In the early phase, leptospirosis typically presents as an ***acute onset of fever, myalgia, and headache***. ***Calf tenderness*** and ***conjunctival suffusion*** are characteristic of leptospirosis, but are not always present. Other symptoms include anorexia, nausea, vomiting, abdominal pain, dizziness, lethargy, malaise, arthralgia, eye pain, and photophobia. Rashes include macular, papular and urticariform rashes, mostly on the trunk or pre-tibial areas. Symptoms in the early phase are non-specific and often difficult to distinguish from other causes of acute febrile illnesses.

LATE PHASE: In the late phase, symptoms relate to severe complications involving one or more organs or systems:

Acute lung injury – Pulmonary haemorrhage and/or acute respiratory distress syndrome (ARDS) are associated with very high mortality rates, and are major causes of leptospirosis-related deaths in Fiji. Massive pulmonary haemorrhage can develop very quickly and result in death within hours. Warning symptoms and signs include cough, shortness of breath, blood-stained sputum, haemoptysis, and chest pain. Early recognition of pulmonary involvement is crucial so that referral to Division Hospital and/or ICU can be arranged as promptly as possible.

Acute renal failure – Urine output could be normal, increased, or decreased depending on the stage of renal failure. In the early stages, urine output is usually normal with hypokalaemia. Dialysis is required for severe cases with acute tubular necrosis and oliguria.

Liver involvement – Jaundice can be very intense and associated with poor prognosis, *but is not always present*. Hepatosplenomegaly might be present. It is important to note that severe lung injury and acute renal failure can occur in the absence of jaundice.

Haemorrhagic manifestations – Bruising or bleeding, including epistaxis, conjunctival haemorrhage, haematemesis, melaena, and rectal bleeding.

Myocarditis – Arrhythmias (AF, supraventricular or ventricular extrasystoles), hypotension, cardiogenic shock.

Neurological complications – Drowsiness, confusion, delirium, hallucinations, meningeal irritation, photophobia. Leptospirosis can also cause aseptic meningitis, encephalitis, convulsions, Guillain-Barré Syndrome, transverse myelitis, and other uncommon neurological syndromes.

3.2. RED FLAGS – DANGER SIGNS and SYMPTOMS

The following symptoms, signs, and laboratory findings in a patient with suspected leptospirosis are associated with serious illness and a high risk of poor outcomes and death. If ANY of the following are present, **URGENT TREATMENT AND APPROPRIATE REFERRAL** are required.

- Respiratory: Cough, blood-stained sputum, haemoptysis, shortness of breath, chest pain, or abnormal CXR. Any symptoms and signs could signal pulmonary complications, which can progress rapidly to massive pulmonary haemorrhage, a major cause of leptospirosis-related deaths.
- Bleeding or coagulopathy: petechiae, bruises, GI bleeding, platelets <100,000/mm^3, high prothrombin time, raised INR.
- Abnormal urine output – oliguria or polyuria
- Hypotension – systolic BP <90mmHg or mean BP (MAP) <60mmHg
- Jaundice
- Cardiac arrhythmias
- Neurological involvement: drowsiness, meningism, seizures, focal symptoms/signs

3.3. DIFFERENTIAL DIAGNOSES

Clinical presentation of leptospirosis can be non-specific and difficult to distinguish from other causes of acute febrile illness. A high index of clinical suspicion is therefore important. In Fiji, the most important differential diagnoses include **dengue**, **typhoid**, and **sepsis** (mostly caused by staphylococcal infections). Other differential diagnoses include influenza, pneumonia, arboviral infections (Chikungunya, Zika), rickettsial infections, acute viral hepatitis, pyelonephritis, and meningitis. In patients with haemorrhagic manifestations, severe dengue and meningococcal infection should be considered. Co-infections could also occur, especially during concurrent outbreaks of multiple diseases, e.g. post-flooding outbreaks of leptospirosis, typhoid, and dengue.

Malaria is not endemic in Fiji, but is an important differential diagnosis in patients who have travelled to malaria-endemic areas in the previous 12 months, including India, Vanuatu, Solomon Islands, Papua New Guinea, and sub-Saharan Africa (military personnel). Malaria should also be considered in visitors from malaria-endemic areas, e.g. international students, foreign workers, and sailors.

4. CASE DEFINITIONS

Cases are defined as ***suspected, probable***, or ***confirmed*** (see Figure 3) based on:

- Clinical assessment of symptoms and signs, and
- Epidemiological risk factors, and
- Results of leptospirosis diagnostic tests

The definition of a **SUSPECTED CASE** is based entirely on clinical assessment. If a patient fits the criteria for a suspected case:

- Treatment should be started immediately – see Section 7
- Treatment should not be delayed if diagnostic tests are not available
- Treatment should be continued even if the results of leptospirosis diagnostic tests are negative because serological tests sometimes produce false negative results. **It is also important to note that serological tests (including the Rapid Diagnostic Test and ELISA IgM currently available in Fiji) detect antibodies that appear from the 5th to 7th day from the onset of illness**. The tests are therefore not useful in the first 5 days of an illness.
- Consider referral to higher levels of medical care – see Section 5

Definitions for **PROBABLE** and **CONFIRMED CASES** are based on a combination of clinical assessment and results of leptospirosis diagnostic tests. Suspected cases might be re-classified as probable or confirmed once results of the diagnostic tests are available. Re-classification might therefore need to be done after the patient has recovered, been discharged, or died. Correct classification of cases is important for disease notification and public health surveillance of leptospirosis.

As of December 2015, diagnostic tests used to define probable cases are available in Fiji, but none of the tests used to define confirmed cases are available. *Leptospira* PCR might be available at Mataika House in the future.

The limitations of clinical case definitions should also be noted. It is not possible for a clinical case definition to identify all cases of leptospirosis, or to exclude all cases that are not caused by leptospirosis. The case definition is designed to help distinguish leptospirosis from other common causes of acute febrile illnesses in Fiji, such as dengue and typhoid. In the early phase of leptospirosis, symptoms and signs are non-specific, and it is therefore possible for a patient to have leptospirosis even if they do not fit the case definition**. If leptospirosis is considered as a likely differential diagnosis, treatment can be started even if the patient does not fit the case definition.**

CASE DEFINITIONS for LEPTOSPIROSIS: Suspected, Probable, Confirmed

A. SUSPECTED CASE = **All 3** of the following criteria fulfilled.
Note that a suspected case is defined by clinical assessment alone.

Criteria 1. Acute onset of fever (≥38°C) , headache, and myalgia

Criteria 2. At least one of the following clinical features:

- Conjunctival suffusion (red eyes)
- Jaundice (yellow eyes)
- Acute renal failure (increased or decreased urine output)
- Haemoptysis or blood-stained sputum
- Other bleeding including gastrointestinal bleeding, epistaxis, petechiae

Criteria 3. At least one epidemiological risk factor in the past 3 weeks:

- Occupation: farmer, abattoir worker, outdoor worker, cleaning streams, exposure to sewage & garbage
- Contact with animals: livestock (especially pigs), rodents, pets, wildlife
- Contact with floodwaters or during the post-flood period
- Contact with other freshwater, soil or mud: rivers, lakes, waterfalls, gardens
- Living conditions: live in rural area or village, no metered water at home
- Live or work in a current hotspot area, e.g. recent clusters or outbreaks
- Link to a recent leptospirosis case, e.g. household member, co-worker

B. PROBABLE CASE = suspected case with at least one of the following:

- Positive Rapid Diagnostic Test (SD *Leptospira* IgM) [1]
- Positive *Leptospira* ELISA IgM (Panbio) [2]

C. CONFIRMED CASE [3] = suspected case with at least one of the following:

- Positive *Leptospira* PCR [4]
- Microscopic agglutination test (MAT) [5]: Single sample with titre of ≥ 1:400, or a 4-fold rise in titres between samples taken 14 to 60 days apart
- Isolation of leptospires by culture [5]
- Identification of leptospires in tissues [5]

[1] Available at laboratories across Fiji
[2] Available at Mataika House only
[3] As at December 2015, none of the confirmatory tests were available in Fiji
[4] PCR might be available at Mataika House in the future
[5] Not available in Fiji in 2015

Figure 3. Case definitions for leptospirosis: suspected, probable, and confirm

5. CRITERIA FOR HOSPITALISATION AND ICU MANAGEMENT

The level of care required should be initially determined based on history and examination, and reviewed regularly based on results of investigations and/or any changes in clinical status.

Table 1 shows the four levels of care recommended based on clinical assessment and investigations:

- Level 1: Outpatient management
- Level 2: Inpatient management at Sub-Divisional Hospital
- Level 3: Inpatient management at Divisional Hospital
- Level 4: Intensive care (ICU) management at Divisional Hospital

For patients who fit the case definition of leptospirosis, hospital admission is recommended for most cases because complications can develop quickly and the patient's condition can deteriorate rapidly. These recommendations are particularly important for patients who live in rural and remote areas, or have difficulty returning for re-assessment. The recommendations for level of care are based on clinical best practice, but logistic difficulties might be encountered, e.g. arranging urgent transfers of patients from remote islands to a Divisional Hospital.

In December 2015, there were 3 Divisional Hospitals with ICUs (CWMH, Labasa, and Lautoka), 18 Sub-divisional Hospitals and 5 specialised/private hospitals in Fiji.

Table 1. Levels of medical care recommended based on clinical assessment and investigations

DANGER SIGNS & SYMPTOMS

Increasing disease severity

LEVEL 1: **Outpatient care** if patient fulfills ALL of the following criteria:	**LEVEL 2:** **Inpatient care at Sub-divisional Hospital** if:	**LEVEL 3:** **Inpatient care at Divisional Hospital** if ANY of the following:	**LEVEL 4:** **ICU management** if ANY of the following:
No cough or other respiratory symptoms	No cough or other respiratory symptoms	▪ Cough ▪ Shortness of breath ▪ RR >20/min	▪ RR >28/min ▪ O_2 sat <90% on 6L of O_2 by mask – need non-invasive ventilation ▪ Haemoptysis or blood-stained sputum ▪ Abnormal CXR
Normal BP	Normal BP	▪ Systolic BP <90mmHg	▪ Systolic BP <90mmHg despite adequate fluid replacement
No signs of bleeding	No signs of bleeding	▪ Any signs of bleeding ▪ Platelets <100,000/mm^3 ▪ Increased prothrombin time and/or INR	▪ Haemoptysis or blood-stained sputum ▪ Gastrointestinal bleeding ▪ Platelets <50,000/mm^3
Normal urine output	Normal urine output	▪ Acute renal failure (oliguria or polyuria) ▪ Electrolyte imbalance	▪ Haemodialysis should be considered if any of: • Urea >30 mmol/L • pH <7.2 • Potassium >5.5 mmol/L • Anuria or severe oliguria • Volume overload with pulmonary oedema
No jaundice	No jaundice	▪ Jaundice	
Normal heart rate and rhythm	Normal heart rate and rhythm	▪ Cardiac arrhythmias	
Normal consciousness	Normal consciousness	▪ Altered consciousness	▪ Glasgow Coma Score ≤12 ▪ Seizures
No vomiting	Vomiting and needs IV antibiotics or fluids		
Ambulatory	Not ambulatory		

6. INVESTIGATIONS

6.1. General investigations

Investigations should include full blood count (FBC), urea, electrolytes, & creatinine (UEC), and liver function tests (LFT). Other tests should be considered based on clinical assessment.

Table 2. Common investigations and results in leptospirosis patients

Investigation	Common findings in leptospirosis
FBC	Leucocytosis, neutrophilia with left shift, normochromic anaemia, thrombocytopenia.
UEC	Raised urea and creatinine if renal impairment. Potassium usually normal or low. High potassium is associated with poor outcomes. Low sodium.
LFT	Raised bilirubin (mainly direct), may take time to resolve. Normal or raised liver enzymes. AST and ALT could be 3 to 5 times above normal.
Urinalysis	Proteinuria, microscopic haematuria, pyuria, granular casts.
CPK	Raised in patients with myalgia.
Coagulation	Prothrombin Time (PT), partial thromboplastin time (PTT), and INR may be raised.
ABG	Low PaO_2, SaO_2, PaO_2/FiO_2ratio. Metabolic acidosis (low pH, low HCO_3).
ECG	Atrial fibrillation (AF), supraventricular or ventricular extrasystoles, AV block, others.
Chest x-ray	Variable findings, including alveolar infiltrates, nodular densities and consolidation. Changes could be diffuse or lobar, unilateral or bilateral. Findings could represent a range of pathology, including alveolar haemorrhage, ARDS, or pulmonary oedema.
Lumbar puncture	Neutrophilic or lymphocytic pleocytosis. Mild elevations in protein. Normal glucose.

6.2. Diagnostic tests for leptospirosis

Table 3 provides a comparison of commonly used leptospirosis laboratory tests. As at December 2015, the only two leptospirosis diagnostic tests available in Fiji were:

1. **Rapid diagnostic test (RDT)** (SD *Leptospira* IgM) – available in laboratories across Fiji
2. ***Leptospira* ELISA IgM** (Panbio) – only available at Mataika House in Suva

Important notes about the RDT and ELISA IgM:

- Both tests detect *Leptospira* IgM antibodies, which do not appear until at least 5 days after the onset of illness. ***In the first 5 days of illness, a negative test is not useful for excluding a diagnosis of leptospirosis.*** If onset of illness is definitely less than 5 days, RDT and ELISA should not be used, particularly if there are limited supplies of test kits and/or reagents. Supplies can be quickly depleted during outbreaks, e.g. post-flooding.
- ***Because RDT and ELISA IgM are not useful in the first 5 days of illness, diagnosis and management of suspected cases should be based on clinical assessment.***
- If a patient fits the case definition for suspected leptospirosis, treatment should not be stopped if results of RDT and/or ELISA IgM are negative.
- If initial RDT or ELISA IgM negative, the test should be repeated after 2 to 3 weeks.

Leptospira* PCR** might be available at Mataika House in the future. PCR has the advantages of providing a diagnosis in the first week of illness, and for defining a ***confirmed case.

Table 3. Comparison of leptospirosis diagnostic tests (As at December 2015, only the first two tests on the list are available in Fiji)

Laboratory test	Availability in Fiji in December 2015	Advantages	Disadvantages	Specimen required	Best time to collect specimen	Collection and transport requirements
Rapid diagnostic test (SD *Leptospira* IgM)	Available in laboratories across Fiji	Easy to perform. Result available in ~20 minutes.	Sensitivity & specificity variable.	Whole blood, serum or plasma	At least 5 days from onset of illness	Transport on ice (4°C). Whole blood should be stored at 2 to 8°C and used within 3 days. Serum or plasma should be stored at 2 to 8°C, or frozen if stored for longer than 2 weeks.
ELISA IgM (Panbio)	Available at Mataika House only	Commercial kits, easy to perform. Result available in 1-2 hours.	Sensitivity & specificity variable.	Serum	At least 5 days from onset of illness	Transport on ice (4°C). Storage at 2 to 8°C. If not used within 2 days, serum should be frozen (-20°C).
The following leptospirosis laboratory tests were not available in Fiji in Dec 2015. PCR might be available in the future.						
PCR	Will possibly be available at Mataika House in the future.	Provides confirmed diagnosis at early stage of illness.	Requires expensive equipment and expertise.	Serum or plasma	Within 1st week of illness	Frozen serum (-20°C)
Microscopic Agglutination Test (MAT)	Not available in Fiji. Regional laboratories where MAT available include Brisbane, New Caledonia, and Massey University, New Zealand.	Gold standard serological test. Serogroup specific. High sensitivity and specificity.	Complex to perform. Laboratory needs to maintain panels of live cultures of leptospires.	Serum	After 1st week of illness. Ideally paired samples collected 14 to 21 days apart (max 60 days)	Discuss with receiving laboratory if sending samples overeas. Frozen serum (-20°C) required.
Culture	Not currently performed in Fiji.	Provides definitive diagnosis.	Takes weeks or months to culture, therefore not useful for informing clinical management. Expertise required.	Blood or CSF or urine	Blood and CSF: within 1st week of illness. Urine: 2nd to 4th week of illness. Specimen preferably collected before antibiotic treatment.	Discuss with receiving laboratory in if sending samples overseas.
Histopathology and immunohisto-chemistry	Not available in Fiji.	Leptospires visualised in tissue. Provides early and confirmed diagnosis.	Poor sensitivity and specificity. High concentration of leptospires required for identification by dark field microscopy	Tissue	Post-mortem	Discuss with receiving laboratory if sending samples overseas.

7. TREATMENT

If a patient fits the definition for a suspected case, treatment should be started immediately. Treatment should not be delayed if leptospirosis diagnostic tests are not available, or while waiting for laboratory results. All patients who fit the criteria for suspected leptospirosis should be given antibiotics. Table 1 helps to determine the level of care required.

The limitations of clinical case definitions should also be noted (see Section 4 Case definitions). ***If leptospirosis is considered as a likely differential diagnosis, treatment can be started even if the patient does not fit the case definition.***

7.1. ANTIBIOTICS

All cases of suspected leptospirosis should be treated with antibiotics. Mild cases can be treated with oral antibiotics, but severe cases required IV antibiotics for at least 7 days.

Table 4. Recommended antibiotics and dosages for the treatment of leptospirosis

a) ORAL ANTIBIOTICS – for treatment of mild cases

	ADULTS	CHILDREN
1st choices	▪ **Doxycycline*** 100mg bd for 7days OR ▪ **Amoxycillin** 500mg tds for 7 days	▪ **Amoxycillin** 50mg/kg/day, divide into 8 hourly doses, for 7 days
Alternatives	▪ Erythromycin 500mg qid for 7 days ▪ Azithromycin 1g, followed by 500mg bd for 2 days ▪ Clarithromycin 500mg bd for 7 days	▪ Erythromycin12.5mg/kg/dose (max 500mg/dose) 8 hourly for 7 days

*Note: Doxycycline should not be used in pregnancy, breastfeeding, or children <9yo

b) INTRAVENOUS ANTIBIOTICS – for treatment of severe cases, at least 7 days

	ADULTS	CHILDREN
1st choices	▪ **Crystalline Penicillin G** 1.2g (2 mega units) 6 hourly	▪ **Crystalline Penicillin G** 30 to 50 mg/kg 6 hourly
Alternatives	▪ Ceftriaxone 1 to 2g daily **Use 1st line in ICU, or if suspect typhoid** (2g daily) ▪ Ampicillin – 1 to 2g 6 hourly ▪ Cefotaxime 1g 6 hourly ▪ Erythromycin 500mg 6 hourly (slow infusion)	▪ Ceftriaxone 100mg/kg (max 2g) daily Use 1st line in ICU, or if suspect typhoid or meningococcal ▪ Ampicillin 50mg/kg (max 2g) 6 hourly ▪ Cefotaxime 25mg/kg 6 hourly ▪ Erythromycin 25mg/kg 6 hourly (slow infusion)

7.2. MANAGEMENT OF COMPLICATIONS

The following sections provide guidelines for treating complications that are commonly seen in severe cases of leptospirosis. For management of patients with atypical complications or comorbidities, it is important to use clinical judgement, seek advice from consultants, and refer to higher levels of care if indicated (see Table 1). Many of the recommended treatments below are only possible at Divisional Hospitals or ICU.

7.2.1. DEHYDRATION, HYPOTENSION, AND SHOCK

- Fluid replacement with **IV normal saline 0.9%**
  - Assess hydration clinically and review hourly
  - Beware of excessive rehydration in patients with respiratory complications and/or cardiac insufficiency
- If **systolic BP remains <90mmHg** despite adequate rehydration, or deteriorating hypotension and shock, recommend:
  - Inotropic support as per standard guidelines, using **Adrenaline** or **Noradrenaline** or **Dopamine**. Aim for systolic BP of ≥ 90mmHg, or mean BP (MAP) of 65 to 75 mmHg.
  - ICU admission
- In patients with adrenal insufficiency associated with severe shock, consider adrenal supplementation doses of **Hydrocortisone**: 100mg IV, then 50mg tds.
- **Jarish-Herxheimer** reactions [14] can occur from 1 to 48 hours after the first dose of antibiotics given for leptospirosis, and has been reported with penicillins as well as cephalosporins. It is caused by an acute inflammatory response to the release of large amounts of cytokines when spirochetes are killed. Common features are sudden onset of shivering or rigors, rise in temperature, and hypotension.

7.2.2. RESPIRATORY COMPLICATIONS

- Acute lung injury include **massive pulmonary haemorrhage** and **ARDS**
- **Monitor O_2 saturation**. Arterial blood gases (ABG) should be done whenever possible. If ABG not available, use pulse oximeter to monitor O_2 saturation.
  - If O_2 saturation <90% in ambient air, provide oxygen via mask and titrate flow to maintain O_2 saturation >90%
  - If O_2 saturation <90% in 6L of O_2 via mask, refer to ICU for non-invasive ventilation
- Respiratory complications are associated with very high mortality rates and clinical status can deteriorate very rapidly. Need **URGENT REFERRAL TO ICU** if ANY of the following:
  - RR >28/min
  - O_2 saturation <90% on 6L of O_2 by mask
  - Haemoptysis or blood-stained sputum
  - Abnormal CXR (can range from infiltrates to consolidation of one or more lobes)
- Indications for intubation and protective ventilation include:
  - No improvement in O_2 saturation despite non-invasive ventilation with CPAP or BIPAP
  - Severe ARDS: PaO_2/FiO_2 ratio (PF ratio) <100

- Special notes on protective ventilation of leptospirosis patients:
  - Use low tidal volumes (6 mL/kg) and plateau pressure <30cm of water to reduce the risk of barotrauma
  - Use an initial PEEP of 5 cm of water, and increase as required to maintain PaO_2 >60mmHg, $SatO_2$ >90% and PaO_2/FiO_2 ratio >200.
  - Use intermittent inline suctioning to minimise bleeding
  - Ensure that heat and moisture exchanger (HME) is not blocked with blood

7.2.3. ACUTE RENAL FAILURE

- Maintain **hydration and electrolyte balance**. Give fluid replacement with IV normal saline 0.9%, and assess hydration based on clinical examination and urine output. Continue to monitor and reassess hourly regarding the need for **haemodialysis**. If needed, haemodialysis should be commenced as soon as possible, especially in patients with pulmonary complications.
- **Haemodialysis** is indicated if one or more of the following:
  - Urea >30 mmol/L
  - pH <7.2
  - Potassium >5.5 mmol/L
  - No urine output for 12 hours or severe oliguria (<400mL/day or <0.5mL/kg/hour)
  - Volume overload with pulmonary oedema
- **Adjust dosages of medications** based on creatinine clearance

7.2.4. CARDIAC ARRHYTHMIAS

- Myocarditis can cause a range of arrhythmias including atrial fibrillation (AF), supraventricular, and ventricular extrasystoles, and others
- Important to correct electrolyte imbalances to avoid exacerbation of arrhythmias
- Treat specific arrhythmias according to standard protocols

7.2.5. HAEMORRHAGE & COAGULOPATHY

- **ICU admission** recommended if haemoptysis, blood-stained sputum, GI bleeding, or platelet count <50,000/mm^3
- **Platelet transfusion** recommended if platelet count <50,000/mm^3, particularly if any of the following:
  - Evidence of bleeding (pulmonary, gastrointestinal, or other)
  - Abnormal CXR
  - Invasive procedures are required, e.g. insertion of central venous catheter

  Aim for platelet count of ≥100,000/mm^3
- **Fresh frozen plasma (FFP)** and **cryoprecipitate** should be considered if INR >2 or Prothrombin time >16 sec
- If not eating, give prophylaxis for GI haemorrhage: **Ranitidine** 50 mg IV 8 hourly

7.2.6. STEROIDS

- A recent systematic review [15] found **no robust scientific evidence** to support the use of high (immunosuppressive) doses of corticosteroids in the treatment of severe leptospirosis
- One randomised controlled trial found that high dose steroids were ineffective for severe leptospirosis, and increased the risk of **nosocomial infections** [16]
- A small number of studies reported benefit in using high dose steriods for severe cases, but all had significant methodological limitations (small sample sizes, lack of control group, retrospective studies, diagnostic criteria, unvalidated clinical scoring systems, young patients, and other biases) [15]
- In patients with adrenal insufficiency associated with severe shock, consider adrenal supplementation doses of **Hydrocortisone**: 100mg IV, then 50mg tds

7.3. CONVALESCENCE and FOLLOW-UP

- Patients should not be discharged until all complications and danger signs have resolved.
- Jaundice can persist for many weeks – it is not necessary to wait until jaundice is resolved before discharging a patient if all else is satisfactory.
- Chronic uveitis (iritis, iridocyclitis and chorioretinitis) is a complication of leptospirosis, and can occur up to 18 months after an acute infection.
- If *Leptospira IgM* negative on latest blood sample, arrange for patient to have repeat serology in 2-3 weeks.
- Advise patients to return for review if any deterioration in clinical condition or development of complications and danger signs or symptoms.
- Advise close contacts (e.g. household members, co-workers) to seek early medical attention for any febrile illness.

8. PROPHYLACTIC ANTIBIOTICS

- Currently, there is **little evidence on the effectiveness** of prophylactic antibiotics [17]. Routine use of prophylactic antibiotics is not recommended, but might be used in special situations based on clinical decision on a case-by-case basis.
- **Pre-exposure prophylaxis** for short-term intense exposures, e.g. soldiers, outbreak response personnel, occupational/recreational exposures: **Doxycycline 200mg weekly** starting 1-2 days before exposure and continue during exposure.
- **Post-exposure prophylaxis** after high-risk exposure, e.g. contact with floodwaters with open cuts/wounds in a high risk area: Doxycycline 200mg daily for 3 to 5 days
- Doxycycline is contraindicated in pregnancy, breastfeeding, and children <9 years old. Gastrointestinal side effects are common.

9. DISEASE NOTIFICATION and PUBLIC HEALTH RESPONSE

Leptospirosis is a notifiable disease in Fiji, and reported through the Notifiable Diseases Surveillance System (NDSS). All SUSPECTED, PROBABLE, and CONFIRMED cases and deaths need to be reported as per the **Fiji National Notifiable Disease Protocols.**. Accurate reporting of cases is important for surveillance, identification of hotspots and outbreaks, and initiation of public health responses if indicated.

- **Single cases** of leptospirosis should be notified weekly using routine procedures
- **Clusters of cases or an outbreak** should be reported urgently by telephone to the respective Divisional Medical Officer
- When notifying a case, it is important to include the following information:
  - Classification of the case as suspected, probable, or confirmed (based on case definitions in Section 4, Figure 3)
  - Date of onset of illness
  - Date of presentation
  - Date of collection of blood sample for leptospirosis diagnostic tests
  - Epidemiological links to other cases, e.g. household member, another person from the same community, co-worker
- Laboratories are required to report cases with positive leptospirosis diagnostic tests
- For cases diagnosed at hospitals, Medical Officers should also notify the **Infection Control Nurse**, who will then notify the Divisional Medical Officer (DMO) or Sub-divisional Medical Officer (SDMO). If indicated, the DMO or SDMO will initiate a case investigation by the Divisional or Sub-divisional Outbreak Response Team (DORT or SORT). The teams consist of a Medical Officer, Health Inspector (Environmental Health Officers), and Risk Manager (DORT) or Health Sister (SORT).
- **Case investigations** should include details on patient demographics, history of the illness, type of community where the patient lives, household environment, occupational exposures, contact with animals, and exposure to fresh water and/or flood waters. In hospitalised patients, case investigations should be commenced while the patient is still in hospital. Some patients will be very difficult to contact after discharge, especially those who live in rural and remote areas.
- A standardised **case investigation form** has been developed for leptospirosis (**Appendix G**). Completed forms should be submitted to SDMOs and DMOs.

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