

Diagnostic approach in leptospirosis patients

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Abstract. Leptospirosis is as a worldwide zoonotic disease, spread by pathogenic species of the bacterial genus *Leptospira* that occurs most commonly in tropical and subtropical regions which are one of endemic diseases in some places in Indonesia. The *leptospira serovars* are naturally carried in the renal tubules of rodents, wild and domestic animals. Human can be infected either through direct contact with urine of infected animals or indirect contact through with contaminated water and soil. Clinical manifestation is highly variable. The most cases are with a mild *flu-like illness* which may mimic many other diseases. Weil's disease is the name given to severe illness and is characterized by a severe febrile illness with bleeding, jaundice and renal failure with high mortality rate. Leptospirosis has been frequently underdiagnosed and underreported. The diagnosis of leptospirosis is difficult to confirm and laboratory test is rarely available even in endemic areas.

1. Introduction

Leptospirosis is a neglected zoonotic disease caused by pathogenic spirochetes of the genus *leptospira*. The pathogenesis particularly that of severe disease, remains poorly understood even though Weil published a clinical description of leptospirosis in 1866. It is considered the most common zoonosis in the world and is associated with rodent in setting of poor sanitation, especially after heavy rain or flooding due to storm, agricultural occupations, and increasingly adventure sport involving fresh water, mud, or soil exposure. The organism can remain in renal tubules of rodent and pass through the urine for long period of time, even for the lifetime of the animal. Human infection follows exposure to infected animals, either directly or indirectly through contaminated water and soil. Characteristic of disease is a broad spectrum of clinical manifestation, varying from asymptomatic infection to fulminant, fatal disease. Most of cases are mild form, leptospirosis may present as an acute febrile illness with a biphasic course. Nonspecific symptoms such as fever, headache, myalgia, nausea and vomiting are often confused with viral illness. While a minority develop a severe illness, characterized by jaundice, renal dysfunction, and hemorrhagic diathesis is known as Weil's syndrome. It is often rapidly progressive and is associated with high mortality rate.[1-4]

2. Etiology

The causative agents belong to the genus *leptospira*, highly-motile, fine spiral bacteria of 0.1 µm in diameter and x 6-25 µm in length. Under dark ground microscopy, the organism appears straight with one or both ends hooked.[1] The genus of *leptospira* comprises two species: *L. interrogans* (pathogenic) and *L. biflexa* (saprophytic). Pathogenic *Leptospira* species are divided into serovars according to their antigenic composition. *L. interrogans* included more than 250 serovars.[4] Inada isolated and identified *leptospira* as the etiologic agent also linked rats to disease transmission. Many



different given local names are recognized e.g. mud, swamp, sugar cane, fort Bragg, and Japanese autumnal fevers. *Leptospira* can survive for some days or weeks in a warm, damp, and slightly alkaline condition.[1-4,9]

3. Epidemiology

Leptospirosis is a clinical entity, it is often underdiagnosed and underreported. Current information on global human leptospirosis varies but indicates that approximately 1 million severe cases occur per year, with a mean case-fatality rate of nearly 10%. [4] Most cases occur in men. An estimated 100-200 cases are identified annually in the United States, with about 50% of cases in Hawaii. Indonesia as a country with high leptospirosis cases, third rank of mortality rate in the world. Indonesia Ministry of Health reported there were 641 human cases in 2013 with case-fatality rate was 9.36%. Epidemic of leptospirosis are not well understood. Outbreaks may result from exposure to flood waters contaminated by urine from infected animal, as has been reported from several countries. Recreational exposure and domestic animal contact are prominent sources of leptospirosis. Occupational exposure probably accounts for leptospirosis.[1,2,8]

4. Pathogenesis

Leptospirosis is caused by spirochetes of the genus called *Leptospira*, particularly the pathogenic *Leptospira interrogans* species. This pathogenic species is further subdivided into different serogroups, serovars and strains based on the embedded antigens. Transmission of the pathogen typically includes contact of infected rodent urine through mucous membranes (ie. eye, nose, mouth) and skin lesions. Following the entry, pathogen disseminate through systemic circulation to distant vessels and organs. Virulence factors exist that favors invasion of *Leptospira*, such as hyaluronidase as well as a structural hooked ends and axial flagella, enabling 'burrowing motility' for deep penetration. Bacterial endotoxin, hemolysin and lipase also triggers inflammatory cascade leading to various disease manifestations. *Leptospira* is found in large, or medium vessels or capillaries. On a cellular level, endothelial damage is commonly observed and serves as an underlying cause of endothelial edema, necrosis, or lymphocytic infiltration which constitute systemic vasculitis. Capillary vasculitis is also prominent in all affected organs. Consequently, erythrocyte and fluid loss occurs through enlarged junctions and fenestrae leading to secondary injury.

Organ involvement is frequent, mainly kidneys, lungs and liver. In kidneys, *Leptospira* migrate to interstitium, renal tubules and tubular lumen causing diffuse tubule interstitial inflammation as well as tubular necrosis. Within the lungs, *Leptospira* causes alveolar and interstitial vascular damage with subsequent hemorrhage. This lung involvement is typically associated with leptospirosis-related death. Liver involvement is also common, characterized by centrilobular necrosis and kupffer cell proliferation which may cause jaundice due to hepatocellular dysfunction. Other than aforementioned organs, in severe disease, other organs may also be affected causing myocarditis, meningoencephalitis or uveitis.[1-4]

5. Clinical Features

Manifestations of Leptospirosis is categorized into two distinct types: anicteric and icteric. In anicteric manifestation, infection is typically self-limited, with mild flu-like syndromes that do not require specific therapy. Whilst in the icteric type, known as Weil disease, infection is severe and typically involves multi organ dysfunction or even failure. Clinical course of leptospirosis is described as biphasic, involving acute bacteremia phase and secondary immune phase. Incubation period generally lasts from 5 – 12 days (ranging from 2 – 30 days).

5.1. The acute bacteremia phase

Following the bacterial migration into the blood stream, leptospiremia occurs. Clinically this phase is characterized by a sudden onset of fever (could up to 39⁰-40⁰), with other accompanied flu-like symptoms such as chilliness, headache, sore throat, myalgia, nausea, and vomiting. More burdensome

symptoms such as cough, hemoptysis, dyspnea, abdominal pain with persistent vomiting may also occurs. In some severe form, aseptic meningitis can develop. During this leptospiremia, pathogen can be isolated through blood, cerebrospinal fluid and other tissues, but not from urine. Serology test frequently remains negative of up to at least 5 days prior onset of symptoms.

This bacteremia phase lasts approximately for 4 – 7 days. Subsequent dissemination to organs may follow in this phase, which might include meninges. Myalgia is severe particularly in calves, back and abdominal muscles. Liver is moderately enlarged in this stage commonly without spleen enlargement. Hematologically, platelet count typically falls potentially causing thrombocytopenic purpura or frank bleeding. Serum creatinine increases, with normal creatinine clearance unless tubular necrosis or glomerulonephritis already develop; with accompanied proteinuria in urinalysis.

5.2. The secondary (immune) phase

In this later immune phase, which occurs immediately or within 2-3 days after, the patient generates antibodies towards *Leptospira*. The antibody response mainly involve IgM class that displays strong agglutination properties and could last for up to several months. During mild infection, signs and symptoms may not be as apparent. However in more severe cases, meningeal or hepatorenal manifestation is predominant. In such severe form, septicemia and immune phase typically merge and is difficult to distinguish clinically, showing persistently high fever, jaundice, frank hemorrhage into skin, mucous membranes or lungs. Hepatomegaly and icteric sclera are clinically more noticeable in this phase. The suffused vessels become orange. Purpura and ecchymosis are visible. Renal failure develop, causing oliguria, with accompanied shock, and myocarditis. Pulmonary edema and pulmonary hemorrhage with hemoptysis may also occur which highly associated with mortality.

In oliguric or later anuric patients, plasma creatinin is commonly elevated that typically requires renal dialysis. Potassium level is contradictory low. Bilirubin level is high but liver enzyme usually remains normal or mildly elevated. Thus the presence of high bilirubin and creatinine level should raise possibility of leptospirosis infection. Renal failure commonly cause further deterioration that leads to death, however other underlying causes include myocarditis (showing abnormal electrocardiography), hemorrhage, adrenal failure and cerebral artery thrombosis. In surviving patients without dialysis support, creatinin level begins to decline at the end of the second week prior onset of disease. This process occurs as rapid resolution of tubular necrosis begins. Additionally, renal function parameter is expected to return to normal in 6 months, except the urine-concentrating ability[1-5].

The clinical manifestations are highly variable. In general, the disease presents in four broad clinical categories[6]:

- A mild, influenza-like illness
- Weil's syndrome characterized by jaundice, renal failure, hemorrhage and myocarditis with arrhythmias
- Meningitis/meningoencephalitis
- Pulmonary hemorrhage with respiratory failure

The typical course of leptospirosis with an acute septicemic phase followed by the immune phase as shown in Figure 1.

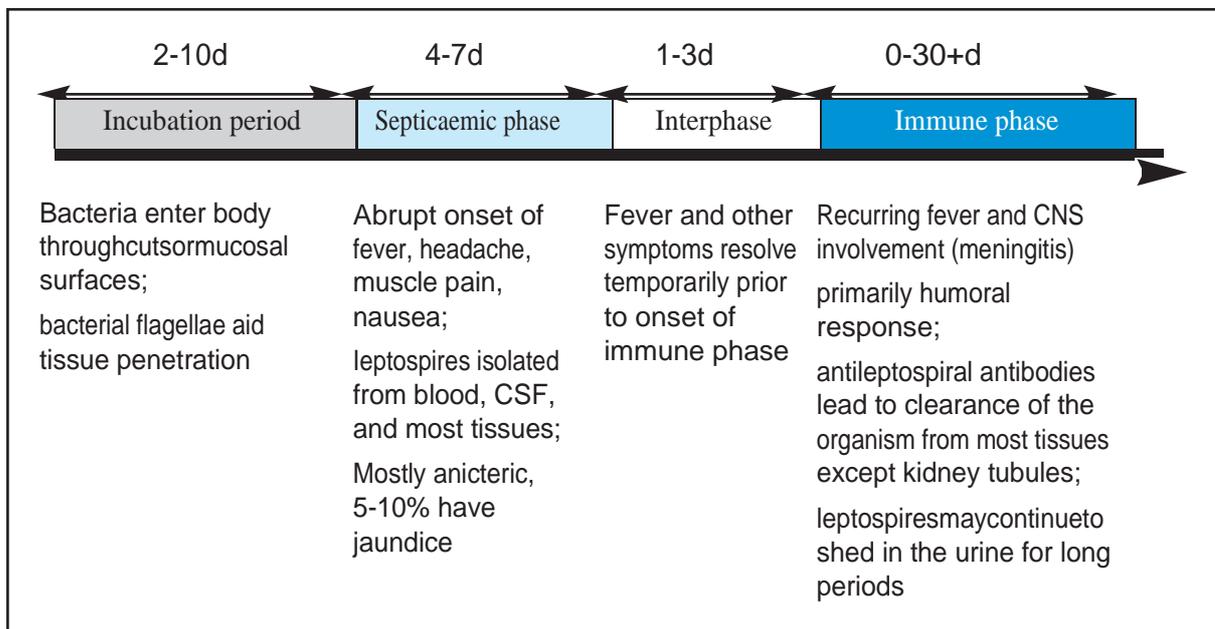


Figure 1. Typical course of leptospirosis[6].

6. Diagnosis

A good clinical history is often the key to accurate diagnosis in leptospirosis. The problem in the diagnosis of leptospirosis are most cases underdiagnosed because symptoms and sign are often nonspecific and serologic confirmation is rarely available. Laboratory studies are used for the purposes[4,5]:

- To confirm the diagnosis and to determine the extent of organ involvement and severity of complication
- For epidemiological and public health reasons, namely to determine which serovar caused the infection, the likely source of infection and the potential reservoir and its location. This help control strategy

Laboratory studies used to diagnosis of leptospirosis include the following:

- *Leptospira* immunoglobulin M (IgM) ELISA or IgM/immunoglobulin G (IgG) enzyme linked immune absorbant assay (ELISA), including rapid diagnostic kits usable in the field
- Real-time DNA polymerase chain reaction (PCR) of blood, urine, and cerebrospinal fluid (CSF)
- Microscopic agglutination testing (MAT); criteria standard for serologic identification of *leptospira*, available at reference laboratories, Single titer $\geq 1:200$ or 4-fold rise in serum drawn between the first and fourth week of illness is considered diagnostic
- DNA PCR of blood, urine, CSF, tissue
- Culture of *leptospira* from body fluids or tissue (criterion standard, but requires specific media and several weeks' incubation, thus usually limited to reference laboratory)

Studies to determine the extent of organ involvement and severity of complications may include the following, depending on the clinical presentation: complete blood cell (CBC) count, renal function test, coagulation test, liver function test, CSF analysis, chest radiography, biliary tract ultrasonography, Electrocardiography (ECG).[1,2,4,5]

Table 1. The WHO-SEA guidelines of leptospirosis diagnostic[7].

Suspected	Probable (At primary health care level)	Confirmed
<p>Acute febrile illness (>38.5°C) And/or severe headache with:</p> <ul style="list-style-type: none"> • Myalgia • Prostration AND/OR • Conjunctival suffusion, AND • History of exposure to leptospira-contaminated environment 	<p>Suspect case with any two of the following:</p> <ul style="list-style-type: none"> • Calf tenderness • Cough with or without hemoptysis • Jaundice • Hemorrhagic manifestations • Meningeal irritation • Anuria/oliguria and/or proteinuria • Breathlessness • Cardiac arrhythmias • Skin rashes <p>Probable (At secondary and tertiary health care levels)</p> <ul style="list-style-type: none"> • Base on availability of laboratory facilities a probable case of leptospirosis is a suspect case with a positive rapid IgM test AND OR supportive serologic findings (i.e, a MAT titer equal 200 in a single sample and or any three following • Urinary findings: proteinuria, pus cells, blood • Relative neutrophilia (>80%) with lymphopenia • Platelets <100.000/cu mm • Elevated serum bilirubin > 2mg %: liver enzymes moderately • Raised serum alkaline phosphatase, S amylase, CPK 	<p>A confirmed case of Leptospirosis is a suspect or probable case with any one of the following:</p> <ul style="list-style-type: none"> • Isolation of leptospirosis from clinical specimen • Positive PCR result • Sero-conversion from a negative to positive or four-fold rise in titer by MAT • Titer MAT of 400 and greater in a single sample

7. Treatment

Antimicrobial therapy is indicated for the severe leptospirosis, but its use is controversial for the mild form of leptospirosis.[4-7]

Table 2. Treatment and chemoprophylaxis of leptospirosis.

Purpose of Drug Administration	Regimen
<p>Treatment</p> <ul style="list-style-type: none"> • Mild Leptospirosis 	<p>Doxycycline 100 mg orally bid or Ampicillin 500-700 mg orally qid or Amoxicilin 500 mg orally qid Azithromycin or clarithromycin Ciprofloxacin or levofloxacin</p>
<ul style="list-style-type: none"> • Moderate/severe leptospirosis 	<p>Penicilin G 1.5 million units IV qid or Ampicilin 1 g IV qid or Amoxicilin 1 g IV qid or Ceftriaxone 1 g IV once daily or Cefotaxime 1 g IV qid or Erythromycin 500 mg IV qid</p>

Chemoprophylaxis

Doxycycline 200 mg orally once a week
Azithromycin 250 mg orally or twice a week

Peritoneal dialysis or hemodialysis should be provided to patients with oliguric renal failure that has been shown to reduce mortality risk and typically and necessary only for short periods.

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