Objectives

■ Understand the importance of early recognition of leptospirosis.
■ Recognize the possible clinical presentations and consequences of leptospirosis.
■ Describe the disease physiopathology and diagnostic criteria.
■ Provide the antibiotic treatment and support required by patients with severe manifestations of leptospirosis.

Case Study

A 43-year-old male taxi driver is evaluated in the emergency department for a 3-day history of fatigue, feverish feeling (unquantified), generalized muscle pain, headache, liquid bowel movements, dark brown urine, and dyspnea. He is a recovering alcoholic who stopped drinking 8 months ago. He has no previous history of allergies to medications, never had a blood transfusion, and has a 1-pack-year smoking history. He has taken only acetaminophen to manage his symptoms.

On admission, blood pressure is 120/60 mm Hg, heart rate 104 beats/min, respiratory rate 39 breaths/min, oxygen saturation 91% on room air, and temperature 36°C (96.8°F). He is diaphoretic, pale, and jaundiced. He had mild hyperemia of the pharyngeal mucosa and mild conjunctival injection. Lung fields are clear. His abdomen is soft and not tender, with no hepatosplenomegaly or adenopathy.
On admission, laboratory results are: hemoglobin 113 g/L, hematocrit 32.6%, leukocytes $8.9 \times 10^9/L$ (3% lymphocytes, 7% monocytes, 50% segmented neutrophils, 40% banded neutrophils), platelets $20 \times 10^9/L$, prothrombin 85%, partial thromboplastin time 39.7 sec, urea nitrogen 43 mg/dL, creatinine 3.88 mg/dL, lactate dehydrogenase 304 U/L, creatine kinase 6316 U/L, total bilirubin 7.75 mg/dL, direct bilirubin 5.08 mg/dL, indirect bilirubin 2.67 mg/dL, aspartate aminotransferase 277 U/L, alanine aminotransferase 116 U/L, alkaline phosphatase 94 U/L, and gamma-glutamyl transpeptidase 176 U/L.

Arterial blood gas measurements are: pH 7.34, $P_{O_2}$ 52 mm Hg, $P_{CO_2}$ 27.8 mm Hg, bicarbonate 18.3 mEq/L, and oxygen saturation 87%.

Urinalysis reveals: density 1005, occult blood +++, leukocytes countless, erythrocytes countless, remaining findings negative.

Serologic findings are: *Leptospira* immunoglobulin (Ig) M, negative; hepatitis A, B, and C, negative; cytomegalovirus IgM, negative.

After these findings are obtained, the patient is interviewed again. He reports that he was working at a construction site 10 days ago. The environment was humid, contained stagnant water, and was infested with rats, cats, and dogs.

The patient was admitted to the ICU where he soon deteriorates, developing respiratory failure and severe hypotension with signs of hypoperfusion. He is intubated, and mechanical ventilation and vasopressor support are initiated.

- Does the patient have signs of either acute or chronic sepsis?
- Which systems are affected most severely?
- What is the epidemiologic link? Does it correlate to the clinical presentation?
- What is the diagnostic value of the *Leptospira* serology in relation to the evolution of the disease?
I. INTRODUCTION

Leptospirosis is an infectious disease caused by pathogenic spirochetes of the genus *Leptospira* (derived from the Greek *lepto* or *thin* and *spira* or *coil*). Some *Leptospira* are pathogenic, such as *Leptospira interrogans*, while others are nonpathogenic saprophytes, such as *Leptospira biflexa*. Twenty-one new species are catalogued with DNA recombination that may be pathogenic to humans. The most severe presentation of leptospirosis was described by Adolf Weil in Heidelberg, Germany in 1886, and is therefore known as Weil disease.

*Leptospira* can cause a mild, nonspecific presentation or a severe one associated with multisystem compromise and high mortality. The organism has global distribution, mainly in tropical or subtropical regions with a humid, rainy climate. Its natural reservoirs are the kidneys of infected mammals, mainly rodents. Infection in humans occurs by direct contact with the tissue or urine of infected animals or, more frequently, indirectly by contact with water or soil contaminated by urine from infected animals. Some examples of those susceptible to contact are farmers, cattle ranchers, veterinarians, construction workers, fishermen, adventure sportsmen, swimmers, and nature tourists. The bacteria can enter through the conjunctiva, oral mucosa, intestinal tract, wounds, or abrasions, with dissemination to the central nervous system, vitreous humor, lungs, heart, liver, and kidneys. The bacteria can also produce vasculitis, which enables infection of all tissues.

The infection rate is considered to be underestimated because leptospirosis has a wide range of presentations and can be similar to a flu-like illness. In subtropical countries, the rate can be 0.1 to 1 per 100,000. In rainy tropical countries, the rate can rise to 10 to 100 cases per 100,000. In periods of thunderstorms and subsequent river or sewage flooding, the rate can reach 100 per 100,000.

Leptospirosis is a disease with specific treatments and an excellent recovery rate, even in the most severe presentations. It should be included in the differential diagnosis of a patient with a febrile syndrome in endemic or epidemic regions.
II. DIAGNOSIS

High clinical suspicion is the pivotal point for the diagnosis of leptospirosis. It can cause the following conditions:

1. Mild disease similar to a flu-like illness

2. Weil disease, characterized by jaundice, renal failure, bleeding, and myocarditis associated with dysrhythmias

3. Pulmonary hemorrhage and respiratory failure

4. Meningoencephalitis and aseptic meningitis

Clinical and laboratory study abnormalities will depend on the affected organs.

A. Clinical Manifestations

The incubation period for *Leptospira* is usually 10 days, but may vary from 5 to 14 days. Two phases are classically described:

1. Leptospiremic phase, during which bacteria disseminate through the bloodstream to the organs and body tissues; this usually occurs within 5 to 7 days. Death is rare at this stage, and the symptoms may resolve.

2. Immunologic phase, during which maximal organ injury occurs; it can be fatal.

The clinical presentation may be nonspecific with generalized signs and symptoms, such as abrupt fever (38°C-40°C [100.4°F-104°F]), chills, generalized myalgia, headache, anorexia, asthenia, conjunctival injection without exudates, coughing, pharyngitis, vomiting, abdominal pain, and watery diarrhea. Less frequently seen in this phase are lymphadenopathies, hepatomegaly, and splenomegaly.

The immunologic phase can start between days 4 and 30 after the initial phase. An increase is seen in the titer of the specific *Leptospira*
IgM. The patient may develop renal failure, jaundice, cardiac dysrhythmias, aseptic meningitis, conjunctival injection (with or without hemorrhage), ocular pain, myalgia, adenopathy, and hepatosplenomegaly.

Manifestations will be related to the disease severity and affected organs. Subclinical presentations are possible.

1. Weil Disease

This is the most severe presentation of leptospirosis. The most frequently affected systems are:

- Renal: The primary manifestation consists of nonoliguric renal failure associated with hypokalemia and hyponatremia due to increased fluid loss and no reabsorption. Urea nitrogen is usually below 100 mg/dL, and creatinine between 2 and 8 mg/dL. If not treated aggressively with fluid replacement, the patient may develop oliguria. Tubulointerstitial nephritis and glomerulonephritis are caused by immune complexes.

- Hepatic: Liver histopathologic findings do not correlate with the increased bilirubin levels, which can rise to 80 mg/dL, with transaminase levels below 200 U/L. Other manifestations include degeneration of hepatocytes, Kupffer cell hypertrophy, erythrophagocytosis, cholestasis, mononuclear infiltrates, and an absence of necrotic foci.

- Hematologic: Leptospirosis appears as peripheral leukocytosis with a left shift and mainly as thrombocytopenia in the absence of disseminated intravascular coagulation.

- Cardiovascular: Cardiac failure is uncommon; the main manifestations are dysrhythmia and nonspecific electrocardiographic changes, often atrial fibrillation, sinus tachycardia, atrial flutter, and premature ventricular complexes. A sudden cardiovascular collapse can occur, which requires aggressive support. Histologic findings are interstitial myocarditis with involvement of the conduction system, as well as coronary arteritis and aortitis.
2. Severe Pulmonary Hemorrhage Syndrome

This complication is usually associated with Weil disease or is the only manifestation. The symptoms appear early, mainly as dyspnea or coughing and sometimes hemoptysis, which is seldom detected until the patient is intubated. The radiologic findings are caused by bilateral lower lobe infiltrates and progress to global alveolar infiltrates.

Clinically this syndrome is consistent with acute respiratory distress syndrome associated with the hemodynamics of septic shock. Histopathologic examination shows injury to the capillary endothelium with intra-alveolar and interstitial hemorrhage, an absence of inflammatory infiltrates, and severe disruption of the air spaces.

3. Meningoencephalitis and/or Aseptic Meningitis

This condition occurs in 80% of patients with leptospirosis and is manifested by an intense pulsating headache located in the frontal and bitemporal regions and by neck stiffness; it may be associated with delirium. Cerebrospinal fluid reveals mild pleocytosis and a lymphocyte count below 500/mm³, mild increase in proteins (50-100 mg/mL), and a normal glucose level. Neurologic manifestations are not frequently described, such as transverse myelitis, hemiplegia, Guillain-Barré syndrome, and severe meningoencephalitis.

B. Laboratory Diagnosis

Several detection techniques for the isolation of spirochetes, as well diagnostic tests for the disease, have been developed. Their value depends on the stage of the disease and whether the patient has received antibiotics.

1. Direct detection methods: *Leptospira* can be seen in the leptospiremic phase in urine and blood using a darkfield microscope, though the method is not very sensitive (40.2%) or specific (61.2%). The use of other direct techniques is not widespread. The most sensitive detection method is polymerase chain reaction (PCR), which can be helpful early in disease development or as a confirmation tool.
2. Cultures and identification: The culture sample must be obtained during the febrile phase in the 10 first days of the disease and before the patient has received antibiotics. Isolation is possible in cerebrospinal fluid, blood, and peritoneal fluid. The sample should be placed in the culture medium immediately after being collected (ie, at the patient’s bedside). The urine test is performed on a sample obtained after a week of symptom development. The sample should be processed in less than an hour because the viability of the bacteria in an acid medium is poor. After isolation, the microorganism should be serotyped according to the antigens.

3. Indirect detection methods: The methods used most often are the microscopic agglutination test and the detection of Leptospira IgM. This is a live antigen test; agglutination occurs when the bacteria come in contact with the serum of an infected patient. Results are considered positive when the serotype titers increase fourfold during the course of the disease. Its greatest limitation is poor sensitivity in the initial phases; Leptospira can be determined after day 5 of symptom onset.

### III. MANAGEMENT

The severe presentations of leptospirosis require monitoring and an approach to the affected systems that includes an early start and aggressive support measures. Infected patients recover completely.

Admission to the ICU: The biggest challenge is in identifying patients with the most severe forms of leptospirosis, such as Weil disease and severe pulmonary hemorrhage syndrome. The following clinical findings confer a higher risk of death:

1. Age 30 to 40 years and older
2. Acute renal failure (oliguria, hyperkalemia, creatinine ≥3.0–4.0 mg/dL)
3. Respiratory failure (dyspnea, pulmonary rales, radiologic evidence of infiltrates)
4. Hypotension
5. Arrhythmia

6. Altered mental status

Isolation: These patients must be admitted to the ICU. They do not require special isolation measures; however, level 2 biosafety measures must be maintained, especially with body fluids such as blood and urine.

Fluid and electrolyte replacement: From the standpoint of renal compromise, nonoliguric hypokalemic renal failure can be managed with aggressive intravenous fluid replacement and supplemental potassium to avoid oliguric renal failure and severe hypokalemia.

Cardiovascular support: Guidelines for vasopressor use should follow the Surviving Sepsis Campaign guidelines. The target mean arterial pressure should be 65 to 70 mm Hg in adults. Caveats for higher mean arterial pressure in patients with a history of hypertension or inadequate end-organ perfusion should be considered. Norepinephrine is the first-line treatment because of these patients’ higher risk of arrhythmia. Epinephrine is a second-line drug. Dobutamine can be considered for inotropic support. Arrhythmias must be treated according to advanced cardiac life support guidelines.

Liver dysfunction disturbances: A severe elevation of bilirubin levels (above 30–40 mg/dL) is typical, associated with cholestasis and sepsis. Liver function returns to normal with recovery from illness without sequelae.

Acute renal failure: If renal support is required, it must be started early because it has been shown to impact survival; in countries with limited resources, peritoneal dialysis has been used. However, the use of continuous hemofiltration has been shown to be more effective than peritoneal dialysis in treating infection-associated acute renal failure.

Respiratory failure: Ventilatory support, when necessary, is based on pulmonary protection measures, as in acute respiratory distress syndrome, with strategies based on low tidal volumes (<6 mL/kg) and high positive end-expiratory pressure. Nevertheless, the mortality rate for severe pulmonary hemorrhage syndrome is more than 50%.
Pregnancy: *Leptospira* infection can result in miscarriage in more than 50% of patients in some series. Late infections can result in the fetus having active leptospirosis at birth but does not appear to be associated with congenital abnormalities or long-term sequelae in surviving children; as such, leptospirosis acquired in pregnancy is not an indication for termination.

## IV. TREATMENT

Antibiotic treatment must be started as soon as possible (Table 1). *Leptospira* bacteria are very sensitive to antibiotic therapy, which achieves early response and control of the infection. However, most patients present in advanced stages of the disease and often have multiorgan compromise, making the impact of antibiotic therapy difficult to determine.

### Table 1 Leptospirosis Treatment: Selection by Disease Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Antibiotic</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Mild leptospirosis</td>
<td>Doxycycline</td>
<td>100 mg orally twice daily for 5–7 days, or 100 mg IV daily for 7 days</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>500–750 mg orally every 6 h, or 0.5–1 g IV every 6 h</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>500 mg orally every 6 h</td>
</tr>
<tr>
<td></td>
<td>Azithromycin</td>
<td>1 g orally, then 500 mg daily for 2 days</td>
</tr>
<tr>
<td>Moderate to severe leptospirosis</td>
<td>Penicillin G</td>
<td>1.5 million units IV every 6 h</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>500–750 mg orally every 6 h, or 0.5–1 g IV every 6 h</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone</td>
<td>1–2 g IV daily for 7 days</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>100 mg orally, twice daily for 5–7 days, or 100 mg IV daily for 7 days</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Doxycycline</td>
<td>200 mg orally per week</td>
</tr>
</tbody>
</table>

Abbreviation: IV, intravenous
Jarisch-Herxheimer reaction has been described in patients with leptospirosis who have received penicillin and tetracycline. Rigor, fever, and hypotension—which can be severe—occur within 2 hours of administration. The patient should be observed for several hours after receiving treatment.

Other proposed therapies:

1. Steroids: The use of high doses of steroids has been proposed as an option for severe cases of leptospirosis. Treatment plans using methylprednisolone, from 250 mg/day to 1 g/day for 3 days, followed by prednisone, 1 mg/kg/day, show apparent benefit to the patient with severe pulmonary hemorrhage syndrome. However, the evidence is not robust and there is a lack of well-designed studies to show efficacy. Studies of dexamethasone treatment have not shown any benefit.

2. Plasma exchange: Some cases have been reported of patients with elevated creatinine levels and renal failure who were treated with plasmapheresis, resulting in recovery of liver and renal functions. The beneficial effects of plasma exchange could be attributed to amelioration of the toxic effects of hyperbilirubinemia in the hepatocytes and renal tubular cell function.

3. Desmopressin: This medication has been used as adjunct therapy in patients with massive hemoptysis. The level of evidence for it is limited to cases using an infusion of 0.3 µg/kg in 30 mL of saline administered over 30 minutes; this treatment could be repeated two or three times at 12- or 24-hour intervals if minor bleeding occasionally persists.

V. PREVENTION

Disease prevention should be based on avoiding contact with the bacteria while in high-risk environments. A vaccine is useful, but may not be readily available in some countries. Doxycycline, 200 mg weekly, can provide prophylaxis.
Case Study Rationale

- Does the patient have signs of either acute or chronic sepsis?
  Yes, our patient has signs and laboratory findings of sepsis. His Sequential Organ Failure Assessment (SOFA) score is 11 and quick SOFA (qSOFA) score is 1. He also has evidence of compromise of the renal, hepatic, hematologic, and respiratory systems; therefore, he has severe sepsis with an acute presentation.

- Which systems are affected most severely?
  He has multisystemic compromise, initially with severe renal, hematologic, and hepatic failures; this is the most severe presentation of leptospirosis, Weil disease, and is seen before cardiovascular and respiratory failure.

- What is the epidemiologic link? Does it correlate to the clinical presentation?
  The patient reported working at a construction site 10 days ago. The environment was humid, contained stagnant water, and was infested with rats, cats, and dogs. Other high-risk sites are rivers and areas of humid soil. Farmers, cattle ranchers, veterinarians, fishermen, adventure sportsmen, swimmers, and nature tourists are also at high risk of *Leptospira* infection.

- What is the diagnostic value of the *Leptospira* serology in relation to the evolution of the disease?
  The incubation time of *Leptospira* is usually 10 days, but may vary from 5 to 14 days. The immunologic phase is between 4 and 30 days before symptoms appear. This patient’s nonspecific symptoms began 6 to 7 days after his exposure, and he presented within 10 days of his exposure. The disease is in the immunologic phase. Organ compromise is present.
  In the case study, the IgM result was negative at admission (3 days after onset), inconclusive on hospital day 5 (8 days
after onset), and positive on hospital day 8 (10 days after onset). The PCR result was positive, and the disease was confirmed.

**KEY POINTS**

- Leptospirosis, an infectious disease caused by pathogenic *Leptospira*, requires a high level of clinical suspicion and identification of the epidemiologic nexus for diagnosis.

- The clinical presentation of leptospirosis can range from mild and nonspecific to severe and associated with multiorgan compromise and high mortality; however, those infected still have a good chance of complete recovery.

- *Leptospira* is found in tropical and subtropical countries. Its natural reservoirs are infected mammals, especially rodents. Infection occurs via the mucosa or skin lacerations after direct or indirect contact with secretions or urine from infected animals in a humid environment.

- The disease has an incubation period of 7 to 14 days and develops in two phases: leptospiremic (5 to 7 days) and immunologic (4 to 30 days), during which time organ injury can occur.

- There are four classical clinical presentations: mild fever of unspecified origin similar to a cold, Weil disease, severe pulmonary hemorrhage with respiratory failure, and aseptic meningitis/meningoencephalitis.

- Microbiologic diagnosis is difficult because it depends on when the patient seeks care, the disease phase, the type of test used, and the management of the sample.

- PCR is the best diagnostic test for an early and specific diagnosis; however, the specific IgM is not detected until after day 5 of the disease.
Antibiotic treatment can be accomplished with penicillins and cephalosporins, as well as doxycycline and azithromycin, according to the severity of the clinical presentation.

When antibiotic treatment is started, the patient must be monitored for Jarisch-Herxheimer reaction.

Fluid replacement and support for the affected organs must be started early.

Prevention of this zoonotic disease is achieved by avoiding contact with contaminated sites and the prophylactic use of doxycycline, 200 mg weekly.

Suggested Readings


**Suggested Websites**


**Acknowledgment**

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