MANAGEMENT OF WEIL'S DISEASE WITH SEPSIS AND MULTIPLE ORGAN DYSFUNCTION SYNDROME

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Abstract

Leptospirosis is a common zoonotic disease with a wide range of clinical manifestations, specifically in tropical regions. Weil's disease is considered a severe form of leptospirosis seen in a minority of leptospirosis cases with considerable mortality. These patients typically developed multiple organ dysfunction (MOD) of acute kidney injury, jaundice, and ARDS. We reported a case of a 62-year-old male transferred to our intensive care unit due to sepsis, severe leptospirosis jaundice, acute respiratory distress, thrombocytopenia, and renal injury. The patient was successfully managed with appropriate antimicrobial treatment and other supportive management, including mechanical ventilation and renal replacement therapy. Moreover, leptospirosis should be considered in any location wherever risk factors are present, not just in epidemic and tropical areas. In this case, we pointed out that serious complications of leptospirosis, such as multiple organ dysfunction, may happen. In such cases, adopting an integrated multidisciplinary team approach is essential to prevent complications and reduce mortality.

Keywords: Weil's disease, Sepsis, MOD, AKI, ARDS
INTRODUCTION
Tropical diseases account for twenty to thirty percent of the reasons for intensive care unit (ICU) admissions in South America, Africa, and Asia. Leptospirosis was originally identified in the Andaman and Nicobar Islands in 1929, and since then, it has spread to become one of the most common causes of intensive care admissions in underdeveloped nations, according to the World Health Organization (WHO). It is estimated that there are 8,73,000 cases worldwide each year, with 48,600 fatalities. Leptospira interrogans is the bacteria that causes leptospirosis, a zoonotic illness. Illness can result from mucosal contact with the urine of sheep, cattle, wolves, and rodents carrying the infection. Mostly, rats are the reservoir. It is endemic to India, and the end of the monsoon season marks its peak. There is a biphasic clinical presentation. Ninety percent of patients recover during the first phase, known as the "anicteric phase," which lasts for three to seven days and is characterized by fever, chills, headache, anorexia, diarrhea, abdominal discomfort, acute myalgia, and conjunctival suffusion or bleeding. Ten percent of patients experience a recurrence of symptoms within one to three days following initial improvement, which leads to a more severe form of the disease known as "Weils disease." Acute respiratory distress syndrome (ARDS) with pulmonary bleeding, disseminated intravascular coagulation (DIC), multiple organ dysfunction syndrome, and increasingly severe jaundice are the characteristics of this (MODS). This was demonstrated in a 2004 study at Sion Hospital, where 26 patients required ventilator assistance and 46 out of 60 leptospirosis patients suffered MODS, with a 52% mortality rate. The biphasic phase is not clinically visible at this time since most patients with severe leptospirosis develop MODS three to five days after developing a fever.

CASE REPORT
In this case, we had a 62-year-old male patient with Weil's Disease. At the time of admission, the patient complained of shortness of breath 2 days before admission. The patient also suffered from swelling of both legs and increasingly less urination. The patient complained of jaundice of the eyes and whole body since 2-3 days before admission. In addition, the patient also complained of fluctuating fever, accompanied by muscle pain, especially in the calves and waist. There was no history of hemoptysis. The patient often cleans the duck pen behind his house without wearing foot protection, where there are many rats in the duck pen.

The patient's condition at the beginning of hospital admission was somnolent and respiratory distress with oxygen saturation of 90% using a non-rebreathing mask of 10 liters per minute. Intubation and mechanical ventilation were performed and the patient was admitted to the ICU with continuous sedation.

![Figure 1. X-ray Findings](image)
(A) Chest X-ray shows bilateral consolidation in both lungs (day 1). (B and C) Pneumonia improves (Day 7 and 11), (D) Complete resolution of both lungs. Patient can be extubated (Day 18)

An initial laboratory exam reveals acute kidney injury, liver failure, respiratory failure, thrombocytopenia, and metabolic acidosis. (Table 1) Because of the initial presentation and the patient’s occupation, leptospirosis was immediately suspected and treated with antibiotics (ceftriaxone). Thoracic X-ray examination showed consolidation in both lung fields. (Figure 1) Hemodialysis was immediately performed and continued intermittently at a distance of 2 times a week. After several rounds of hemodialysis, serum urea, and creatinine levels improved and urine output gradually normalized. Chest X-ray results also showed that the pneumonia had improved.
DISCUSSION

Risk Stratification of Leptospirosis Patients

Guidelines from the World Health Organization (WHO) recommended the use of the Faine criteria in 1982 for leptospirosis diagnosis and severity evaluation. Three epidemiologic factors (part B), four bacteriologic and laboratory findings, and nine clinical measures (part A) are used in the Faine criteria (part C). The sensitivity and specificity of these criteria are 81.8 and 72.9%, respectively. This criterion is not always possible, though, as it depends on the results of the MAT examination (microscopic agglutination test).

To stratify leptospirosis risk, the THAI LEPTO score was created. This score is made up of seven factors. An ICU admission, mechanical breathing, and inotropic or vasopressor assistance are indicated if the score is greater than six. The three characteristics that make up the SPIRO score, which was also established in Australia, are oliguria as a clinical variable, auscultatory respiratory problems, and systolic blood pressure ≤100 mmHg. Each component is worth one point. In this study, 392 patients (98%) had their SPIRO scores determined. For scores of 0, 1, 2, and 3, the likelihood of a serious illness was 3, 20, 69, and 100%, respectively. A negative predictive value of 97% was found for severe illness for SPIRO scores less than 1. When triaging leptospirosis patients who require critical care, emergency medical personnel can swiftly calculate the SPIRO score instead of the qSOFA score. In emergency treatment, the SPIRO score was demonstrated to be more effective than qSOFA.

Laboratory Investigation in Critical in Critical Patients

Serology is the most common method used to diagnose leptospirosis. On the fifth or seventh day following illness exposure, antibodies start to manifest. The microscopic agglutination test (MAT) has a sensitivity and specificity of 63 and 97%, but the sensitivity and specificity of the IgM ELISA are 89 and 94%. The most common method for diagnosing leptospirosis is serology. It takes up to seven days following disease exposure for antibodies to manifest. IgM ELISA has 89 and 94% sensitivity and specificity, but the microscopic agglutination test (MAT) has 63 and 97% sensitivity and specificity.

<table>
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<tr>
<th>Examination</th>
<th>Result</th>
<th>Day 1</th>
<th>Day 4</th>
<th>Day 7</th>
<th>Day 11</th>
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Abbreviations: ALT = Alanine Aminotransferase; APTT = Activated Partial Thromboplastin Time; AST = Aspartate Aminotransferase; dL = deciliter; g = grams; L = liter; mEq = milliequivalent, min = minutes; mm = millimeter; uL = microliter; PaCO₂ = Partial pressure of Carbon Dioxide in arterial blood; PaO₂ = Partial pressure of Oxygen in arterial blood; HCO₃ = Bicarbonate; U = unit.
Leukocytosis due to sepsis, thrombocytopenia, and occasionally pancytopenia due to macrophage-activating syndrome are all seen on a full blood count (MAS). High D-mimer levels, low fibrinogen, and prolonged PTT all suggest DIC. Serum creatinine, blood urea, bilirubin, and transaminitis levels that are elevated indicate the severity of liver and kidney failure. Hyponatremia, hypokalemia, and hypomagnesemia are examples of aberrant electrolyte levels. Arrhythmias and alterations in the ECG can be brought on by electrolyte imbalances. Glomerulonephritis is indicated by proteinuria, granular casts, and microscopic hematuria on urinalysis. Rhabdomyolysis may result in an increase in serum creatine kinase. Out of 22 CSF samples, 5 had leptospira antibodies. 54 patients (19.65%) with diffuse opacity on thoracic X-rays showed evidence of pulmonary bleeding in a study of 275 leptospirosis patients.

In this case, the diagnosis of leptospirosis was made according to the history and clinical symptoms obtained by the patient. The presence of contact with an at-risk environment accompanied by symptoms of fever, jaundice, and impaired renal function was the basis for the diagnosis of leptospirosis. The patient's SpiRO score was 2, indicating a 69% chance of leptospirosis.

Clinical Presentation and Management of Leptospirosis in ICU

Severe leptospirosis patients need to be managed with intensive care. When patients with severe leptospirosis are admitted to the intensive care unit, they may die from renal failure, ARDS with thrombocytopenia, or MODS.

Icteric Leptospirosis
In one investigation, icteric symptoms (72%), hepatomegaly (67%), transaminitis (81%), and increased bilirubin were identified as hepatic signs (60%). Thus, despite the hemorrhagic phase of the disease, prior observations in leptospirosis-affected patients demonstrated non-specific hepatocellular damage affecting the sinusoidal poles, endoplasmic reticulum, mitochondria, and bile secretion system. Sinusoidal poles exhibit modified microvilli, dilated biliary canaliculi with partial or whole lack of microvilli, and dilated intercellular gaps with secondary microvilli. Glycogen is depleted, microbodies are present, and in more severe cases, smooth endoplasmic reticulum is predominant in hepatocytes. Hepatocytes have dilated intercellular gaps that are home to leptospira remnants and potentially bile pigments. In a leptospirosis experimental hamster model, jaundice was directly caused by leptospira migrating across intercellular connections, indicating disruption to hepatocytic intercellular junctions. When jaundice is induced, bile seeps into the bloodstream from the biliary capillaries.

In this case, the patient was found to be icteric. Jaundice is an important manifestation of liver dysfunction, but its mechanism in leptospirosis is still not fully elucidated. Serum biochemical studies have shown that concentrations of transaminases and to a lesser extent of alkaline phosphatase, are moderately elevated in human leptospirosis. The icteric condition is mainly due to elevated conjugated bilirubin and impaired bile excretion with intrahepatic cholestasis, which at the time appeared to be the main cause.

Acute Kidney Injury
In 16–40% of cases of leptospirosis, acute kidney injury (AKI) develops. Prerenal or renal injury may be the cause of the kidney damage. Hypovolemia and hypotension brought on by third-space fluid loss from leptospirosis-caused vasculitis are examples of prerenal processes. Hypovolemia is made worse by thrombocytopenia-related bleeding. Acute tubulointerstitial nephritis can result from direct tubular damage or from immunological processes triggered by toxins. Tubular damage is a result of rhabdomyolysis brought on by significant myalgia in leptospirosis cases. AKI in leptospirosis is associated with lower serum potassium levels and is non-oliguric. The hypokalemia is explained by an increased sodium load in the medullary collecting tube (MCT), where sodium and potassium exchange takes place, as a result of decreased sodium absorption brought on by proximal tubular injury. The MCT's resistance to vasopressin may be the cause of the non-oliguric character of renal failure.

Correction of AKI resulting from hypovolemia necessitates intravenous saline with cautious potassium administration to prevent adverse consequences from fluid overload. In cases of acute tubular necrosis resulting in non-oliguric renal failure, renal replacement treatment may be necessary (RRT). Cito HD is indicated by laboratory criteria of metabolic acidosis (pH 200 mg/dl, hyperkalemia > 7mEq/Lt) and clinical criteria of poor general condition (uremic encephalopathy, uremic pericarditis, refractory pulmonary edema, fluid overload, anuria > 5 days).

In cases of leptospirosis, starting dialysis is early advantageous and lowers mortality. Thirty-three leptospirosis patients with renal failure participated in an ICU trial in Sao Paulo. Compared to the group receiving late-onset dialysis, the group receiving early dialysis (daily dialysis at the time of hospital admission) experienced a significant reduction in mortality (16.7 vs 66.7%). In comparison to normal peritoneal dialysis, hemodialysis and hemofiltration resulted in faster recovery, decreased mortality, and faster reductions in blood bilirubin, urea, and creatinine levels (Thai study).

Hemodialysis in this case was based on the condition of uremic encephalopathy, metabolic acidosis, and oliguria. After hemodialysis, the patient's condition gradually improved although during treatment in the ICU, the patient needed several hemodialysis treatments until the creatinine and urea level was close to normal.

Acute Respiratory Distress Syndrome (ARDS)
Leptospirosis patients may exhibit dyspnea, cough, mild to severe hemoptysis, or acute respiratory distress syndrome (ARDS). Even in the absence of evident symptoms, diffuse intra-alveolar bleeding may be seen on radiographic imaging. There have been numerous reports of pulmonary radiographic abnormalities in leptospirosis earlier; these changes are typically bilateral. These non-specific patterns might be linked to pneumonia in general or pulmonary bleeding specifically.\textsuperscript{16} In Australian research, moderate to severe ARDS was seen in 58–67% of leptospirosis patients admitted to the intensive care unit. In 49% of these instances, mechanical ventilation was necessary.\textsuperscript{17} In severe leptospirosis, dyspnea, and chest infiltrates are predictors of mortality and markers of a bad prognosis. Individuals who may have alveolar hemorrhage or ARDS need to be on mechanical breathing while using lung-protective techniques.\textsuperscript{2} Although it is uncommon, leptospira-induced severe pneumonia can be extremely dangerous for patients. Many efforts can be done to accurately diagnose the condition, even though it is difficult to distinguish from other infectious diseases due to the lack of identifiable clinical signs and ineffective diagnostic methods. First, patients with severe pneumonia, especially those who have bleeding problems, require close monitoring for signs of Leptospira infection. Second, identifying high-risk individuals who may come into touch with contaminated water or soil, or with potentially infected creatures, will offer compelling evidence for a diagnosis.\textsuperscript{18}

It's possible that the patient's pulmonary bleeding from leptospirosis was the source of their respiratory distress. The possibility of respiratory distress brought on by pneumonia or sepsis process is raised, nonetheless, in the lack of clinical evidence such as hemoptysis.

**Thrombocytopenia**

When there is a leptospira infection, thrombocytopenia and thrombocytosis might happen, particularly if sepsis is present. Leptospirosis is frequently associated with thrombocytopenia, indicating mechanisms involving peripheral platelet consumption from extensive bleeding, immune-mediated platelet death from platelet antibodies, and bone marrow-inhibited platelet synthesis.\textsuperscript{19} In between 40 and 86.6% of cases of leptospirosis, thrombocytopenia is a common finding. Mortality and platelet count have been associated in certain research. Studies on thrombocytopenia and its correlation with other clinical and laboratory results, however, are scarce. Unknown is the precise etiology of thrombocytopenia in leptospirosis. Thrombocytopenia has been linked to vasculitis, reduced platelet production, increased peripheral injury, and increased platelet consumption.\textsuperscript{20–24}

In this case, the patient was found to have thrombocytopenia. However, platelet transfusion has not been given in this case because there are no signs of bleeding or critical values of thrombocytopenia.

**Neurological Manifestation**

Ten to fifteen percent of patients get neurologic symptoms. Patients with leptospirosis who have diminished awareness may also have meningoencephalitis, uremia, hepatic encephalopathy, intracerebral hemorrhage from bleeding diathesis, abnormal electrolyte levels, and subsequent bacterial meningitis. Thirty-one cases of leptospirosis with neurologic symptoms were documented in one investigation. Only three individuals had localized impairments, while 25 patients (81%) had altered sensoriums, and 11 patients (35.5%) experienced acute symptomatic seizures upon presentation. Twenty-six patients (about 26%) passed away. Raised CSF protein and coma at presentation are not good predictors of outcome.\textsuperscript{9}

Patients with leptospirosis may experience diminished awareness due to sepsis or uremic encephalopathy. The treatment of people with this illness is around the use of the right antibiotics and renal replacement therapy to lower serum urea levels.

**Antimicrobial Agents and Corticosteroids in Leptospirosis**

For a duration of seven days, the following antimicrobial medicines are advised: Ceftriaxone (1–2 g IV once daily), Doxycycline (100 mg IV twice daily), Cefotaxime (1 g IV every six hours), and Benzylpenicillin (1.5 million units intravenously every six hours). For two to three weeks, patients with leptospirosis and meningoencephalitis may need a larger dosage of benzylpenicillin (20 L IV at 6 hours).\textsuperscript{3} In a Brazilian intensive care unit research, it was discovered that using ceftriaxone early on could avoid severe leptospirosis. Since resistance is uncommon, testing for antibiotic sensitivity is not done frequently.\textsuperscript{25} An inflammatory response to the clearance of spirochetes referred to as the Jarisch-Herxheimer reaction occurs after treatment. The appearance of fever, chills, and hypotension characterizes it.

Corticosteroids can be beneficial in patients with moderate to severe thrombocytopenia due to leptospirosis. They use prednisolone at a dose of 1 mg/kg for 1 week.\textsuperscript{26} High-dose methylprednisolone IV for 3 days followed by prednisolone 1 mg/kg for 7 days may benefit patients with ARDS and myocarditis.\textsuperscript{27,28} Serial case reports continue to serve as the foundation for data about the use of corticosteroids in leptospirosis. The broad use of this medicine requires the support of randomized controlled studies.

In this case, the antibiotic given was Ceftriaxone. This is in accordance with the recommended antibiotic regimen for the management of leptospirosis. The success of antibiotic therapy was proven by the improvement of the patient's condition while being treated in the ICU.
In a study aimed at lowering leptospirosis patient mortality, it was discovered that corticosteroid medication and intensive care unit treatment were linked to lower mortality. Antibiotic therapy was started during the first six hours of treatment for every subject in the study. Of the 48 patients who experienced AKI, 18 needed replacement therapy (RTT) and 34 needed vasopressor assistance. Corticosteroids were given to twenty patients. Elderly patients with numerous comorbidities made up two of the four percent of the deceased patients.\textsuperscript{17} Even with a high initial SpiRO score, severe leptospirosis had a decreased mortality rate with timely resuscitation, according to another study involving 134 patients.\textsuperscript{29} In a French multicenter study, leukocytosis, invasive ventilation, ethanol addiction, elderly age, and hepatic encephalopathy were linked to the 9% death rate of leptospirosis patients in the intensive care unit. The leptospirosis that resulted in pulmonary hemorrhage with hepatorenal (n = 101, 63%), neurologic (n = 8, 5%), and respiratory problems (n = 17, 11%) had the highest prediction of death.\textsuperscript{30} In another study conducted in Sri Lanka, very high CRP levels, hyperkalemia, metabolic acidosis, and multi-organ system failure were linked to a high mortality rate of 44.4%.\textsuperscript{31}

In this case, the conditions that led to increased mortality were sepsis, ARDS, AKI, hyperbilirubinemia, and thrombocytopenia. However, proper management such as the administration of appropriate antibiotics, mechanical ventilation with lung protective strategy, intermittent hemodialysis, and appropriate nutrition can ultimately save the patient from his critical condition.

CONCLUSION
The implications of this study are notable for many reasons. Leptospirosis continues to be a cause of infection in developing countries. Early recognition is crucial as early antibiotic administration can decrease the severity and duration of the disease and lead to excellent outcomes. This case is reported to remind physicians of rare serious complications such as jaundice, ARDS, renal failure, and thrombocytopenia. A multidisciplinary team discussion is recommended for better patient survival.

REFERENCES
\[2\] Karnik ND, Patankar AS. Leptospirosis in intensive care unit. Indian Journal of Critical Care Medicine. 2021;251(S2).