REVIEW NEPHROLOGY

Acute Kidney Injury and Acute Liver Failure in Leptospira Infection and Weil's Syndrome

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Abstract

Leptospirosis is considered a zoonosis acquired predominantly from contaminated surfaces and water, more commonly in emerging countries with limited sanitary conditions. Leptospira in the host unleashes an immune response that explains the symptoms and clinical signs; once it reaches the kidney and liver tissue, it can manifest with alterations that lead to acute and chronic diseases in both organs. Weil's syndrome is the best known clinical manifestation with jaundice and acute kidney injury that could lead to multiple organ failure and death. For its diagnosis, there are simplified scores such as the SPiRO score, the microbiological criteria by microscopy or serological tests; the treatment focuses on antibiotics and, if necessary, provides organic support until the infection is curtailed. *The purpose of this review was to address the impact of Leptospira infection on the kidney and liver, the mechanisms of organ damage, the clinical presentation, and diagnosis and management of this disease.*

Keywords: leptospirosis; acute kidney injury; acute liver failure

Introduction

Leptospira *shares characteristics of both gram-positive and gram-negative bacteria*, and it is strictly a gram-negative aerobic bacterium belonging to the spirochetes genus. There are 22 species (pathogenic and nonpathogenic), as well as more than 350 serotypes (1) (Figure 1A). Leptospira was first observed more than 100 years ago and has been found in most mammals worldwide, including a kidney sample from a whale (2). It is transmitted to humans via infected animals when they come in contact with, or through, contaminated water. It is a ubiquitous disease, more commonly found in tropical climates and in areas where large reservoirs of stagnant water accumulate (3), such as lakes or water remnants from natural disasters (4) (Figure 1B), *and transplacental infection is rare but possible* (5).

It can result in conditions ranging from a mild and clinically irrelevant disease, to multi-organ failure, with a high mortality rate. In this review, we will describe the epidemiological and clinical aspects of renal and hepatic involvement.
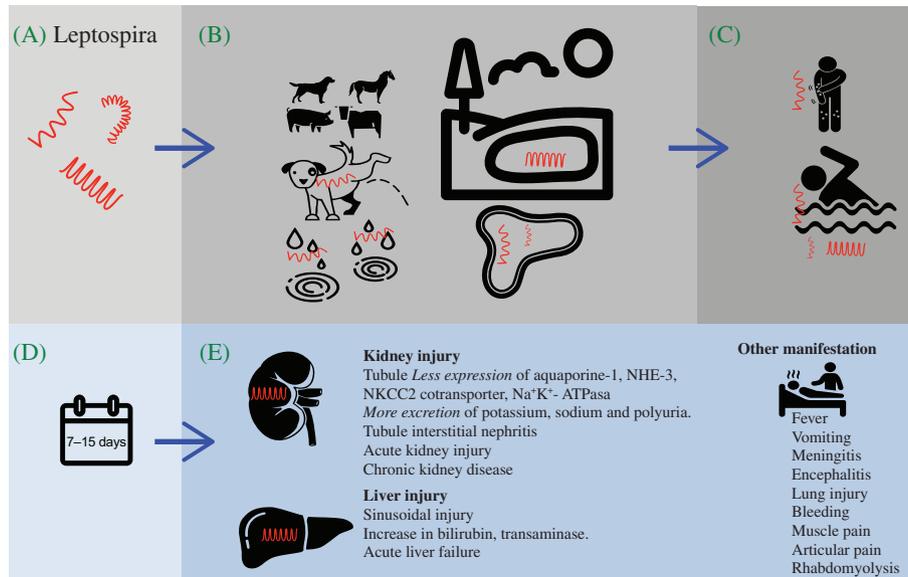
Figure 1. Transmission of Leptospira and the development of leptospirosis with its clinical manifestations: (A) Leptospira are strictly anaerobic bacteria belonging to the spirochetes genus; (B) Leptospira in infected rodents, dogs, pigs, cattle, and horses are the typical vectors; (C) The route of infection is through direct or indirect contact with contaminated tissues, urine, soils or water; (D) The incubation period is usually 8–12 days; (E) Pathophysiological and clinical manifestations of leptospirosis and the Weil's syndrome.

Epidemiology

The incidence of leptospirosis is 10–100 cases per 100,000 population/year in humid tropics. However, the incidence appears to be higher, with some studies reporting a sero-prevalence of anti-Leptospira antibodies of up to 33% in asymptomatic individuals. The World Health Organization has included leptospirosis as a re-emerging infectious disease, and cases have been increasingly reported in developed countries, where rodents, dogs, pigs, cattle, and horses are the typical vectors (6, 7) (Figure 1B). As of 2015, the global incidence of leptospirosis amounted to 1.03 million cases annually, with 58,900 deaths worldwide (8).

The route of infection in animals is usually the same as that in humans, that is, through direct or indirect contact with tissues, urine, soils, or water contaminated by a previously infected individual. When the organism is passed through the infected animal's urine, it can survive in fresh water for up to 16 days, and in soil for almost 24 days (9, 10). Therefore, exposure to animals typical of this area, as well as activities related to water tanks, are risk factors. Patients with a flooded workplace have a high probability of exposure to the infective organism for a longer duration than other locations (11) (Figure 1C). Because of factors such as population growth and poor health conditions, there has been an increase in the incidence of this disease. In addition, it has been reported that different types of Leptospira can co-exist within the same environment. Therefore, monitoring of potentially contaminated areas is found to have public health benefits, thanks to the impact of maintaining a high degree of diagnostic suspicion when outbreaks of pathogenic strains occur, as well as keeping track of antibiotic susceptibility reports (12).

Pathophysiology

Infection in humans usually occurs via mucous membranes or skin abrasions through which microorganisms penetrate the body (Figure 1C). Once inside, the bacteria enter into the lymphatics and then into the blood stream. From the bloodstream, the infection can spread systemically but tends to settle down within the liver and the kidneys (13). Some studies suggest that the clinical course of the disease depends on a relationship between the species, inoculum size and the route of infection, and the clinical course and outcomes of the disease (4, 14).

Leptospira interrogans produces endotoxins that affect the tubulointerstitial cells, and contains lipopolysaccharide, cytotoxic glycolipoprotein (GLP), and lipoprotein (LipL), especially LipL32, which is immunogenic, and has the ability to activate the immune response driven by white blood cells, producing tumor necrosis factor-α and/or proinflammatory interleukins (15).

The host immune response is both humoral and cellular, and "cytokine storm" and "immunosuppression" models have been proposed (16). Although the pathophysiology of leptospirosis consists of a particular network of mechanisms that are not fully understood, there is no reason to consider the septic shock it causes as different from the typical septic shock caused by other bacteria (17). Markers of endothelial activation and immune activation were associated with disease severity in leptospirosis patients, and it has been shown that plasma levels of E-selectin and Von Willebrand Factor (VWF) strongly increased (18). Leptospires can pass between epithelial cells, including those lining the renal tubules, and this could be an important way to reach and colonize the lumen of the proximal tubules. They have the ability to adhere to cell adhesion molecules, membrane proteins, and transmembrane glycoproteins of the endothelium necessary to maintain vascular integrity, which is a pathogenic mechanism on the endothelium itself (which includes the glomerular, cardiac, and hepatic endothelium). Damage to the glycocalyx has also been observed in kidney tissue obtained from infected individuals (19). The damage to the endothelium may be a key factor in pulmonary pathology. By promoting the extravasation of immune cells to the pulmonary alveoli, autoimmune damage may be triggered, which can cause pulmonary edema and hemorrhagic manifestations (19). Furthermore, although most electron microscopy findings are nonspecific and may be related to the sepsis manifestations of the disease, they suggest a marked alteration of the cell membrane (19).

Weil's syndrome

Following an incubation period of 7–12 days, clinical manifestation of leptospirosis ranges from mild febrile syndrome to multi-organ failure (16, 20). Other less specific symptoms, which are reported less frequently, include muscle aches, headaches, colds, and mucosal hemorrhage (21) (Figure 1D and 1E), including influenza (22), pancreatitis (23), and gastrointestinal symptoms, with vomiting and diarrhea, and fatal septic shock (21). There are reports of neurological symptoms such as aseptic meningitis, reversible posterior encephalopathy (24), and focalization symptoms due to intracerebral thrombosis (25) (Figure 1D and 1E). The simultaneous development of hepatic and renal failure, together with hemorrhagic complications (highly severe when they occur in the lungs), is called Weil's syndrome (26, 27), and represents the severe phase of leptospirosis. Weil's syndrome carries a mortality rate between 5% and 15% of the cases (22, 28, 29). Clinically, it presents as an icteric fever and myalgia, with multi-organ involvement (9). In addition to being caused by co-infections with other liver-damaging agents (30), fulminant hepatic failure appears to be linked to endothelial damage in the liver sinuses (31)

and may require liver transplantation (32). The presence of conjunctival icterus, increased creatinine phosphokinase (CPK) levels, and less severe transaminitis suggests the presence of Weil's syndrome, rather than acute liver failure of a different etiology (33). Pulmonary manifestations and a state of shock add to the severity to the clinical syndrome. Mortality can be associated with advanced age, shock, bleeding, steroid use, oliguria, and arrhythmias. The rate of mortality can be reduced with timely administration of antibiotic treatment (9, 34). In the presence of thrombocytopenia, platelet aggregation and phagocytosis of the Kupffer cells should be considered before disseminated intravascular coagulation (35). Although rare, autoimmune hemolytic anemia may appear (27) (Figure 1E). Mortality is significantly higher in older patients with icteric disease or renal failure but is lower in younger, anicteric patients (36). There is definite cardiac involvement in leptospirosis, which, although not symptomatically evident, may add to the morbidity and mortality or contribute to the mortality associated with the disease (37). In patients with severe leptospirosis in tropical Australia, prompt intensive care unit (ICU) support, including early antibiotic administration, protective ventilation strategies, cautious fluid resuscitation, traditional thresholds for renal replacement therapy initiation, and corticosteroid therapy, was associated with a very low case-fatality rate (38). Pulmonary involvement at admission is a strong predictor of mortality among patients with severe leptospirosis (39). There have been reports on the use of veno-venous extracorporeal membrae oxygenation in cases with severe respiratory failure and pulmonary hemorrhage, continuous renal replacement therapy in acute kidney injury (AKI), as well as plasmapheresis and extracorporeal cytokine absorbent therapy (40, 41).

The presence of multi-organ dysfunction syndrome and serum potassium concentration >5.0 were independently associated with mortality in patients with confirmed leptospirosis in a critical care setting (42).

Manifestations in the kidney

In the kidney, the clinical manifestations vary widely from disorders of urine concentration and electrolytes abnormalities, to AKI and chronic kidney disease (CKD).

The Leptospiral GLP appears to influence tubular transport of ions, particularly Na+ and K+ (43). GLP is a potent and specific Na/K-ATPase inhibitor (44). Tubular changes, characterized by high urinary fractional excretion of sodium and potassium, precede the decrease in glomerular filtration rate, which could explain the high prevalence of hypokalemia. Given that hypomagnesemia usually occurs in the first phase of the disease, close monitoring is also recommended (45). Tubulointerstitial nephritis is a common finding in leptospirosis. In his 2010 report, Araujo et al.

observed a decrease in the expression of ATPase of NHE 3, aquaporin-1, and α-Na (+) K (+) ATPase in the cells of the proximal convoluted tubule. The expression of aquaporin-1 was preserved along the thin descending limb of Henle's loop in the outer medulla. The expression of α-Na (+) K (+) ATPase was essentially preserved in the distal tubules, that is, the thick ascending limb of the Henle's loop, macula densa, and distal convoluted tubule. The expression of aquaporin 2 in the collecting tubules was enhanced compared with that in the nonleptospirotic kidneys. NKCC2 cotransport isoform was expressed in the thick ascending limb of Henle's loop and was essentially preserved in the leptospirotic kidneys (46). Primary injury of the proximal convoluted tubules is regarded as the hallmark of the kidney in leptospirosis (47). Sodium and water transport are particularly affected with increased distal potassium excretion, hypokalemia, and polyuria (46).

Kidney injury secondary to rhabdomyolysis and pyelonephritis has also been found. It should be suspected when treating patients with AKI and hyperbilirubinemia (47) who have recently traveled to tropical countries or considered as a differential diagnosis in children with acute fever of infectious origin, with its focus yet to be determined (48).

AKI is the most frequent complication in Weil's disease, and it is caused by a combination of acute tubular necrosis (ATN) and tubulointerstitial nephritis (49). The incidence of leptospirosis-associated AKI is up to 80%, and its severity is associated with increasing mortality (50, 51, 52, 53). Independent risk factors for ICU admission include tachypnea, hypotension, and AKI. Ceftriaxone is a protective factor for ICU admission, suggesting that its use may prevent severe forms of the disease (54). AKI is typically nonoliguric and is associated with hypokalemia. Oliguria, jaundice, and arrhythmias have been shown to be predictors of AKI development. Hypokalemia is commonly observed in tubulointerstitial nephritis (55). During AKI, a Toll-Like receptors (TLR-2)-dependent immune response occurs, triggering inflammation, which can progress to fibrosis (56). Although acute leptospirosis does not induce multi-organ dysfunction, it can be a predisposing factor for progression to CKD if not treated early. CKD can cause proximal tubular dysfunction, which can be observed in agricultural workers with asymptomatic chronic leptospirosis. It has been suggested that this could represent a predisposing factor that only needs a second hit, such as heat stress or severe dehydration, to progress to end-stage renal disease (57). Another hypothesis supporting leptospirosis as a cause of CKD is the recurrence of AKI, hypokalemia, and the constant proinflammatory stimulus; as an example, some authors have considered it as a possible risk factor in chronic kidney disease of unknown etiology (CKDu). In spite of evidence suggesting that there is an association between leptospirosis and CKDu, no definitive conclusions have been drawn as yet (58) (Figure 1E).

Manifestation in the Liver

In icteric leptospirosis, characterized by rapidly progressive clinical course, high serum bilirubin levels together with moderate increase in liver transaminases may occur (20). Of all leptospiral cases, 5%–10% develop a severe form of icterus (26), which is associated with a mortality rate of 5%–15% (59). It remains unclear to what degree the overall liver function is diminished in icteric leptospirosis (59). Bilirubin and other commonly used parameters of hepatic function, such as aminotransferases, albumin, or prothrombin time, are static estimates that cannot assess complex liver functions such as clearance of substances or formation of metabolites (60). Approximately, 90% of Leptospira infections present with nonspecific anicteric clinical picture of fever, which self-limits within a few days. It can later recur as an immune phase (in this phase, aseptic meningitis can occur), when anti-Leptospira antibodies appear (and bacteria can appear via excreted urine) (56) (Figure 1E).

Diagnostic Tests

In the mild form of leptospirosis, routine blood tests results are usually nonspecific (26). In adults with leptospirosis, a simple three-point clinical score—the SPiRO score—appears to reliably identify patients at risk of severe disease. An absence of hypotension, oliguria, or abnormal auscultatory findings—a SPiRO score of zero—was particularly helpful in identifying patients at low risk of severe disease. This score facilitates the recognition of high-risk patients, expediting the initiation of supportive treatment, and prompting consideration to transfer to a referral facility (61).

Since diagnostic methods can be direct or indirect, the best method depends on when it is used (62) (Figure 2). There are various diagnostic methods: those based on microbiology (dark-field microscopy), serology (microscopic agglutination test [MAT], enzyme-linked immunosorbent assay [ELISA], immunofluorescence, hemagglutination, and lateral flow assay), and those based on molecular biology. MAT is the gold standard for serodiagnosis of leptospirosis because of its unsurpassed diagnostic specificity (63, 64). A combination of C-reactive protein (CRP) and ELISA has been proposed to achieve a rapid diagnosis with little margin for error; however, MAT should subsequently be used to identify the serotype for epidemiological purposes (63).

The modified Faine's prediction score is limited by the requirement of specialized tests, which are difficult to conduct in rural areas. In addition, it was developed for patients who required hospitalization. Because of the high prevalence of leptospirosis in rural areas of developing countries (up to 29.5% in high-risk groups) (65) and the lack of the required infrastructure to carry out these tests, a new score, the OPD Lepto score, has been developed. It comprises only
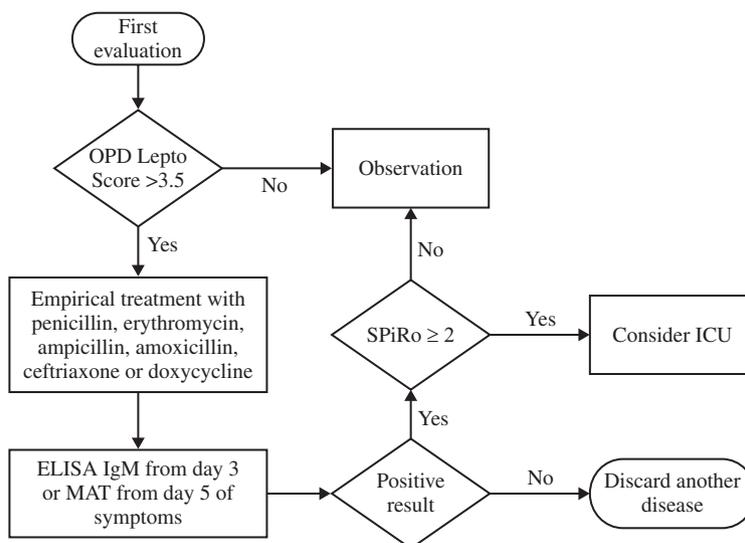
Figure 2. The diagnostic/treatment algorithm for patients at high risk of acquiring leptospirosis, defined as an OPD Lepto Score > 3.5.

five items, which are accessible to the primary care physician, and is feasible in outpatient settings. The maximum score is 7, with 3.5 being the cutoff point to identify patients at high risk of having leptospirosis, requiring prompt intervention to treat the disease (11).

The LeptoDB database incorporates data on genetics, immunology, and possible therapeutic targets (21). Kunikowska et al. described a case of hepatic failure, where dynamic tests, such as indocyanine green plasma (ICG) clearance, reflected more the hepatic functional status. Prolonged elevation in serum bilirubin levels may not adequately reflect recovery of liver injury in this disease. ICG clearance appears to be a promising marker for the detection of hepatic dysfunction and recovery in icteric leptospirosis (66).

Treatment

An approach and treatment algorithm are proposed in Figure 2. Antibiotic treatment is considered efficient in all stages of the disease. Mild cases can be treated in the outpatient setting with oral amoxicillin (30–40 mg/kg/day) or ampicillin (50–100 mg/kg/day) four times a day for 7–10 days. Children > 8 years of age can receive doxycycline (2 mg/kg/dose) two times a day for 7–10 days (62, 63, 67–69). Patients with severe infections should be treated with intravenous penicillin in doses of 50,000–100,000 U/kg/day for 7–10 days, or with third-generation cephalosporins or erythromycin (9). In patients allergic to penicillin, erythromycin, 30–50 mg/kg/day, can be given in 3–4 doses for 7–10 days. Empiric treatment should be recommended before confirmation of laboratory tests, as serological diagnosis is time-consuming (70).

However, a recent study failed to show a decrease in mortality in leptospirotic patients receiving empiric antibiotics (28, 71). Although *Leptospira* spp. are intrinsically resistant to several antibiotics, there is little evidence of acquired resistance to antimicrobial agents used in the treatment of acute leptospirosis (1). Patients experience shaking chills, a rise in temperature, and intensification of skin rashes known as the Jarisch–Herxheimer reaction (JHR), with symptoms resolving a few hours later. Case reports indicate that the JHR can also include uterine contractions in pregnancy, worsening of liver and renal function, acute respiratory distress syndrome, myocardial injury, hypotension, meningitis, alterations in consciousness, seizures, and stroke (72). Two risk factors were independently associated with JHR occurrence: *L. interrogans* serogroup Australis as the infectious agent and a delay of >3 days between the onset of symptoms and the initiation of antibiotherapy (73). Although rarely encountered and not well described in the literature, initiation of antibiotics can cause a JHR reaction. The JHR may be self-limited and of short duration, or it can be prolonged and severe (74). It has been recommended that patients started on antibiotics for leptospirosis/Weil's disease should be monitored in the emergency department for a short period of time, prior to discharge or being admitted to a regular medical ward for observation, given the possibility of decompensation. The use of azithromycin and doxycycline has been shown to decrease seropositivity without a significant effect on clinical leptospirosis (65).

The treatment of Weil's syndrome consists of life support measures and antibiotic therapy (75). It is common for seriously ill patients to require renal support therapy and ICU

monitoring. Treatment recommendations include a high dialysis dose, but the type of dialysis may not affect clinical outcomes in severe leptospirosis (76). Conservative fluid intake and approaches to minimize lung injury, such as low tidal volume and high positive end-expiratory pressure, when artificial ventilation is required, are recommended (28, 77).

Finally, Gomes et al. opened a new window of opportunity to treat leptospirosis with antibodies. They reported that anti-LipL32 mAbs inhibited the growth of *L. interrogans in vitro* and offered significant protection in animal models when administered prior to infection (78).

Acknowledgments

None.

Conflicts of interest

The authors declare no conflict of interest.

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