Leptospirosis-associated acute kidney injury

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Abstract

Leptospirosis is the most important zoonosis in the world. Patients are typically young men. Several factors are involved in acute kidney injury (AKI) in leptospirosis, including direct nephrotoxic action of the leptospira, hyperbilirubinemia, rhabdomyolysis and hypovolemia. The major histological findings are acute interstitial nephritis and acute tubular necrosis. Leptospirosis-induced AKI is usually non-oliguric and hypokalemic. Tubular function abnormalities precede a decline in the glomerular filtration rate, which could explain the high frequency of hypokalemia. Antibiotic treatment is efficient in the early and late and/or severe phases. For critically ill leptospirosis patients, the following measures are recommended: early and daily hemodialysis; low volume infusion (due to the risk of pulmonary hemorrhage); and lung-protective strategies. Mortality in leptospirosis-associated AKI is around 22%.

Keywords: leptospirosis, acute kidney injury, signs and symptoms, pathology, therapeutics.

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Introduction

Leptospirosis is a zoonosis caused by a microorganism of the *Leptospira* genus, an obligate aerobic spirochete of worldwide distribution, with two species: *L. interrogans* (pathogenic) and *L. biflexa* (non-pathogenic and saprophytic). The *L. interrogans* complex is composed of 23 serogroups and approximately 210 serovariants.[1-4] The same serovariant can induce different clinical presentations.[5]

The rat is the major reservoir of leptospira, mainly in urban areas. Transmission to man occurs through direct contact with blood, tissues, organs, or urine of infected animals, or through indirect contact, when injured mucosa or skin is exposed to contaminated water.[1,2,6,7] In tropical countries, leptospirosis is an endemic disease, with outbreaks occurring during the rainy season, coinciding with flooded areas[3]. The incidence of leptospirosis in some endemic countries is increasing. In Thailand, for example, the reported incidence increased 30 times between 1995 and 2000.[8] In Brazil, data from the Health Ministry have shown that, between 1996 and 2005, 33,174 cases of leptospirosis were notified, and, in 2007, 1,547 cases were notified, most of which in the southern region (45.7%) (http://www.datasus.gov.br).

The mean incubation period is of 15 days. The clinical manifestations of leptospirosis may be grouped as follows: (I) self-limited anicteric febrile disease (85%-90% of the cases); (II) Weil syndrome characterized by jaundice, kidney injury, hemorrhage, and myocarditis with arrhythmias (5%-10% of the cases); (III) meningitis/meningoencephalitis; and (IV) pulmonary hemorrhage with respiratory failure.[1,9] The clinical course of leptospirosis can be divided into two phases. The initial phase lasts three to seven days, and the symptoms are high fever, chills, severe headache, followed by anorexia, diarrhea, nauseas, vomiting, malaise, and myalgia, more pronounced in the calf region of the leg. Fever ranges from 38°C to 39°C and subsides after four to seven days from symptom onset. In that phase, leptospira can be isolated in the blood. In some cases

(around 20%), symptoms resume after one to three days, initiating the immune phase of the disease, which lasts four to 30 days. In the second phase, more severe symptoms, such as meningitis and uveitis, can occur. IgM antibodies are commonly found in that phase, and the severity of leptospirosis is associated with the intensity of the humoral immune response of the host.[2,10]

Leptospirosis is an infectious vasculitis. In the severe form, patients can develop hemodynamic alterations secondary to hypovolemia due to dehydration and the direct effects of the toxins that damage the vascular endothelium and increase permeability.[10]

Diagnosis is established based on clinical findings and epidemiological data, being confirmed by laboratory tests. The clinical diagnosis can be difficult, and confusion with the following conditions can occur: dengue; hantavirus hemorrhagic fever; viral or bacterial meningitis; malaria; and viral hepatitis. The presence of hypokalemia, an initial and characteristic finding of leptospirosis, can indicate the diagnosis. Definitive diagnosis is established by isolation of the leptospira, but it is a difficult technique that requires a long period of cultivation, frequently allowing only a retrospective diagnosis. Detection of IgM antibodies by use of enzyme immunoassay (ELISA) has high sensitivity and specificity (around 90% for both), although sensitivity is lower (39%-72%) in the acute phase. Polymerase chain reaction (PCR) is precocious and sensitive, but its high cost and need for high-quality control are the major drawbacks for its application. The most used laboratory method to diagnose leptospirosis is the microscopic agglutination test (MAT), performed from two blood samples collected at a two-week interval. The results are considered positive when antibody titles are four times greater than the reference value. Its efficacy has been recently investigated by the International Society of Leptospirosis, and the rate of false-negative results found was 13%.[2]

Renal involvement

Epidemiology

In developed countries, leptospirosis is an uncommon cause of acute kidney injury (AKI).[11] However, in tropical countries, where the disease is endemic, leptospirosis is an important cause of AKI. The incidence of AKI varies from 10% to 60%, depending on the severity of the disease, age, and definition of AKI.[12] In some countries, such as Thailand and Singapore, leptospirosis accounts for more than 20% of the cases of AKI.[13] In the state of São Paulo, Brazil, 7,374 cases were notified in the past ten years, corresponding to 22.3% of all cases in Brazil (http://www.cve.saude.sp.gov.br, accessed January 10, 2008). At the Hospital das Clínicas of the city of São Paulo, of the 6,777 cases of severe AKI treated in the same period, only 60 had leptospirosis, a prevalence of 0.89% (Abdulkader RCRM, unpublished data). That percentage can be observed at similar hospitals in more developed countries.

Clinical manifestations

Renal involvement in leptospirosis can vary from a subclinical course, with mild proteinuria and urinary sediment abnormalities, to severe AKI. Leukocytes and red blood cells are seen in the urinary sediment. Proteinuria, when present, is usually lower than 1 g/24h. Biliary pigments and granular casts can also be seen.[12]

Acute kidney injury usually presents with a rapid elevation in serum urea and creatinine, and can be associated with jaundice. Kidney injury in patients with hyperbilirubinemia represents a severe form, frequently accompanied by oliguria-anuria.[12]

Acute kidney injury due to leptospirosis usually presents in the non-oliguric form with hypokalemia, which can be detected in 41% to 45% of the patients with leptospirosis associated with AKI.[14]

In a recent study, 58 patients with leptospirosis and AKI had hemorrhagic diathesis (80%), liver failure (72%), respiratory failure (38%), circulatory failure (33%), pancreatitis (25%), and rhabdomyolysis (5%).[15] Arterial hypotension is common.[16,17] The hemodynamic status and alterations in most patients with severe leptospirosis are similar to those observed in patients with sepsis. Because of systemic vasodilation, the plasma levels of aldosterone and antidiuretic hormone are high. Renal vasoconstriction and decrease in diuresis occur.[18]

Tubular dysfunctions, mainly of the proximal tubule, are very common, even in the absence of AKI. Alterations, such as bicarbonaturia, glycosuria, and a reduction in sodium proximal reabsorption and uric acid and phosphate excretion, have been observed, and a deficit in the urinary concentration can persist for prolonged periods.[19]

Hypokalemia is a frequent finding in AKI of leptospirosis, and can be observed in 45% to 74% of patients on hospital admission, requiring intravenous potassium replacement in 80% of the cases. In the AKI of leptospirosis, even oliguric patients do not usually have hyperkalemia. Hypokalemia is the most

characteristic laboratory finding of AKI of leptospirosis. Seguro *et al.*[14] have shown that AKI of leptospirosis is usually non-oliguric and have evidenced hypokalemia in 45% of the cases. Thus, AKI of leptospirosis, regardless of its severity, hypercatabolism, rhabdomyolysis, acidosis, and oliguria, is characterized by normo- or hypokalemia. That is a relevant characteristic of AKI due to leptospirosis at the time of diagnosis.

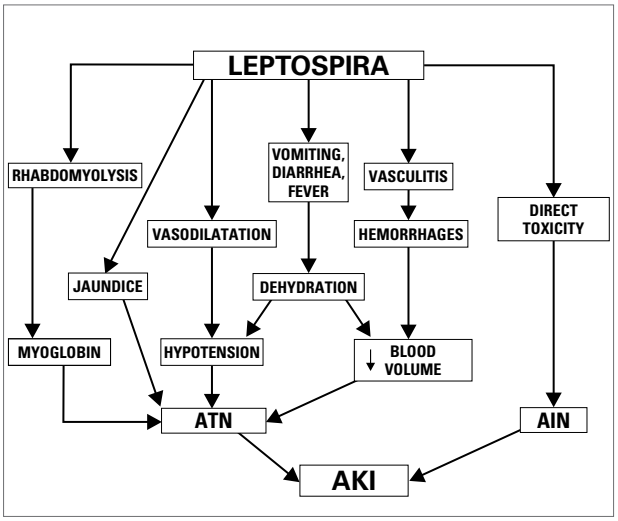
Another early characteristic of kidney injury is the ultrasound finding of enlarged kidneys, with relatively normal parenchymal echogenicity, indicating tubulointerstitial nephritis.[20] The kidneys recover their normal size after the effective treatment of leptospirosis.[21]

Physiopathology

Renal impairment is a frequent complication in patients with the severe form of leptospirosis, mainly characterized by an association of interstitial and tubular damage.[22]

The major factors involved in the pathogenesis of AKI in leptospirosis are the direct nephrotoxic action of the leptospira and the toxin-induced immune response. Hemodynamic alteration, jaundice, and rhabdomyolysis are also associated with the genesis of AKI in leptospirosis (Figure 1).

Figure 1. Physiopathology of AKI in leptospirosis.



Adapted from Abdulkader & Silva.[56]

Acute interstitial nephritis

Experimental studies have shown that AKI is associated with the presence of leptospira in the renal tissue, which triggers a process of acute interstitial nephritis (AIN), which is the major causing mechanism of AKI in that disease.[22] Some studies have suggested that AIN occurs after tubular damage. Patients who died within the first week of the disease had acute tubular necrosis (ATN) and cell edema, while those who died within two to three weeks of disease had ATN and interstitial edema, and those dying after three weeks had severe and diffuse interstitial nephritis.[22] Both lesions are associated with the presence of leptospira antigens in the renal tissue. The presence of that bacterium in the mesangium and renal interstitium has already been observed in experimental studies, three to six hours after inoculation of *L. icterohaemorrhagiae*. The passage of the leptospira through the glomerular capillary causes a mild and transient proliferation of the mesangium. Glomerular alterations are very discrete, consisting of mild mesangial proliferation.

Direct effect of leptospira

Study of the kidney after inoculation of leptospira in rats has shown that entry of the microorganism occurs through penetration of the capillary lumen on the second day, while entry in the interstitial tissue causing edema and cell infiltration occurs between the fourth and eighth day. Leptospira can be identified adhered to the epithelial surface of the renal tubules after the first week and in the tubular lumen in the second week.[23]

Leptospira antigens are found in the cells of the proximal tubule and as large extracellular clusters in the interstitium.[24] Foci of ATN can also be seen.

The outer membrane of leptospira contains antigenic components including lipoproteins, lipopolysaccharides and peptidoglycans, endotoxins that can account for kidney injury, leading to tubular dysfunction and inflammation. Several outer membrane proteins (OMPs) of pathogenic species have been identified and located in the proximal tubules and interstitium of infected animals.[25]

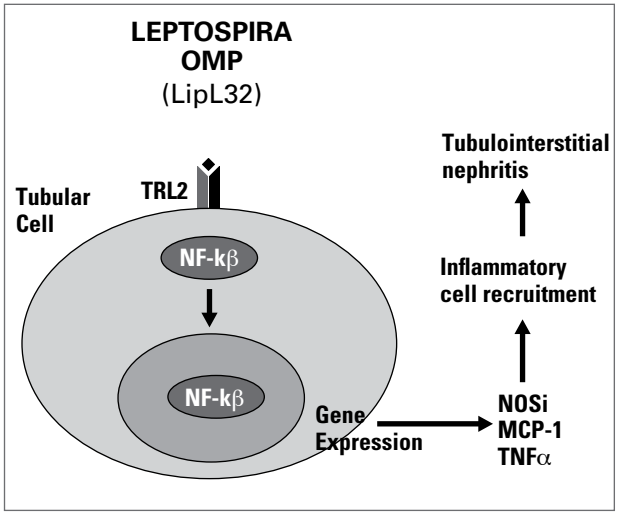
The most important OMP expressed during the infection is LipL32, which affects directly the proximal tubular cells, considerably increasing the expression of genes and pro-inflammatory proteins, such as inducible nitric oxide synthase (iNOS), monocyte chemotactic protein-1 (CCL2/MCP-1), T cells (RANTES), and tumor necrosis factor (TNF-α). The CCL2/MCP-1 chemokine is one of the most important factors at the beginning of the infiltration of monocytes in interstitial nephritis, while TNF-α, an inflammatory cytokine, is a mediator of endotoxemia.

The stimulation of iNOS and CCL2/MCP-1 by OMP, LipL32 in particular, depends on the presence in proximal tubule cells of the toll-like receptor

(TLR), a specific protein that recognizes molecular patterns of pathogens acting as the first line of defense of innate immunity, generating the initial inflammatory response, in this specific case, TLR2.[26]

Briefly, OMP binds to TLR2 in proximal tubule cells, leading to activation of the nuclear factor NF-kβ, which stimulates the production of CCL2/MCP-1 and CXCL2/MIP-2 for recruiting inflammatory cells. The NF-kβ is also associated with the increase in iNOS and TNF-α in proximal tubule cells (Figure 2). [27]

Figure 2. Sketch of the induction and signaling of NF-kβ in tubulointerstitial nephritis caused by leptospirosis.



OMP = outer membrane protein; LipL32 = leptospira lipoprotein antigen; TRL2 = toll-like receptor; NF-kβ = transcription nuclear factor kβ. Adapted from Yang et al.20

Prerenal AKI and hemodynamic alterations

Acute kidney injury in leptospirosis can also have a prerenal component. Hypotension can be observed, because of the reduction in systemic vascular resistance and dehydration.[18] Dehydration is a frequent finding, secondary to fever, vomiting, and diarrhea.[14,28,29] Hypotension can be exacerbated by the decrease in sodium reabsorption in the proximal tubule, characteristic of leptospirosis. After blood volume replacement, the clinical findings improve. Studies have shown that more than 50% of the patients with leptospirosis and AKI respond to venous hydration, improving uremia and oliguria. Hypovolemia can induce an increase in aldosterone and cortisol, despite hypokalemia.[30] Hemorrhagic phenomena mainly attributed to endothelial lesion also contribute to hypovolemia. Thrombocytopenia can exacerbate the tendency to bleeding.[31] A study conducted in Thailand with patients with the severe form of leptospirosis has identified three patterns of hemodynamic alterations.[18] The first pattern, observed in 60% of the cases, was characterized by an increase in cardiac output and a reduction in systemic vascular resistance, resulting in hypotension (pattern similar to that occurring in sepsis and malaria). The hemodynamic alterations of that pattern begin with peripheral vasodilation, induced by cytokines and other mediators, mainly nitric oxide.[18] The second pattern, observed in 20% of the cases, was characterized by normal cardiac output, systemic vascular resistance, and blood pressure, but increased pulmonary vascular resistance. Increased pulmonary vascular resistance can be caused by several factors, including perivascular edema and humoral factors, such as leukotrienes and thromboxane A2.[18] The third pattern was characterized by increased systemic vascular resistance, normal pulmonary vascular resistance, and relatively decreased cardiac output, when compared with those of other patients. The relatively low cardiac output can be caused by hypovolemia or myocarditis, which is described in the severe forms of leptospirosis.[18]

Hyperbilirubinemia

Jaundice is present in almost all cases of severe leptospirosis, and also contributes to AKI. High bilirubin levels lead to alterations in renal function. Sitprija *et al.*[32], analyzing patients with obstructive jaundice due to cholangiocarcinoma, have reported that those with total serum bilirubin greater than 26 mg/dL had a reduction in glomerular filtration and the ability to concentrate urine. High bilirubin levels are common in the severe form of leptospirosis and are associated with the presence and severity of AKI.

Rhabdomyolysis

Myalgia has been observed in almost all cases of leptospirosis, but rhabdomyolysis, detected through the elevation in creatine kinase (CK) levels, has been reported in 45% to 62% of the cases.[10,19,33] The association between rhabdomyolysis and AKI has been well established.[34,35] The major mechanisms of kidney failure secondary to rhabdomyolysis are renal vasoconstriction, tubular obstruction, and direct toxicity of myoglobin.[34] The role played by rhabdomyolysis in the genesis of AKI of leptospirosis is not so evident. High levels of CK are more frequently found in patients with severe AKI than in those with mild AKI, suggesting that rhabdomyolysis can contribute to the severity of AKI.[19]

Tubular alterations

The AKI of leptospirosis is characterized by absence of oliguria, and normal or reduced potassium serum levels, in contrast with AKI of other infectious causes, such as malaria, diphtheria, and meningococcemia.[36,37,38] Experimental and clinical studies have shown that those findings result from injury to the proximal tubule and resistance of the medullary collecting tubule to vasopressin.[14,30,39] The injury of the proximal tubule leads to a reduction in the proximal reabsorption of sodium. The resistance of the medullary collecting tubule to vasopressin leads to a defect in the urinary concentration, causing polyuria. The increase in the secretion of potassium in the distal tubule seems to be determined by an increase in the urinary flow and by an increased sodium offer in the distal tubule, and seems to be potentialized by high levels of aldosterone and cortisol.[30] Those findings show a predominance of the proximal tubule dysfunction and a relative integrity of the distal segments of the nephron regarding the tubular manipulation of sodium and potassium. The OMPs of the leptospira, such as LipL32, activate cascades dependent on toll-like receptors, which lead to the activation of NF-kβ, kinases and cytokines, with subsequent tubular injury. The activation of those mechanisms explains the dysregulation of sodium transporters in the kidneys of leptospira-infected patients.[40,41] Tubular alterations precede the drop in glomerular filtration rate in leptospirosis. A recent experimental study has investigated the alterations in sodium transporters in kidneys and lungs of rats with leptospirosis. Infected animals showed a significant reduction in the expression of the Na^+/H^+ exchanger isoform 3 (NHE3) in the proximal tubule, an increase in the expression of the Na^+K^+2Cl cotransporter (NKCC2), and a reduction in the expression of aquaporin 2 (AQP2) in the medulla.[41] The lungs of the same animals showed a significant reduction in the expression of alpha subunits of epithelial sodium channels (α-ENaC), suggesting a central role of that alteration in the pulmonary edema observed in leptospirosis, since sodium transportation plays a central role in controlling alveolar edema.[41] Clinically, such alterations are translated as manifestations of non-oliguric kidney failure, with an increase in the sodium and potassium fractional excretion, in addition to pulmonary congestion.

Experimental studies have shown that, even in the absence of kidney injury, tubular dysfunction can occur in leptospirosis. A study with leptospira-infected Guinea pigs has shown high potassium fractional excretion and low urinary osmolarity. The collecting tubules of those animals proved to be resistant to vasopressin action.[39] Recently, a clinical study with 20 patients infected with leptospirosis has shown the presence of proteinuria in all cases, hypermagnesuria in 75%, reduced tubular reabsorption in 50%, and reduced phosphate reabsorption in 45% of the patients.[43]

Treatment

Antibiotic therapy

The early diagnosis and institution of appropriate therapy are the most important points in managing leptospirosis. Consensus about the use of antibiotics for treating leptospirosis still lacks.[44-48] A recent meta-analysis has not found sufficient evidence to indicate the use of antibiotics in leptospirosis; however, it concluded that antibiotic therapy in that disease seemed to have more benefits than drawbacks.[44] A recent experimental study has assessed the expression of the NHE3 of the proximal tubule and of the NKCC2 in hamsters with leptospirosis treated or not with ampicillin. The leptospira antigens and the expression of renal transporters were assessed by use of immunohistochemistry and quantification of thiobarbituric acid (TBARS). Antibiotic therapy was associated with a significant reduction in leptospira antigens, normal expression of NHE3 and NKCC2 transporters, and reduced levels of TBARS.[42]

However, clinical studies have shown that antibiotic therapy is efficient in the early and late phases of the disease.[49] Based on the recommendation of the World Health Organization of 2003, severe leptospirosis should be treated with intravenous penicillin (1,500,000 U every 6h), ceftriaxone (1g once a day), or cefotaxime (1g every 6h), all equally effective.[50,51] Antibiotic therapy should be maintained for seven days. Oral antibiotics, such as doxycycline, amoxicillin, ampicillin, erythromycin, or azythromycin are effective in less severe cases of leptospirosis as an alternative for patients with no involvement of vital organs and who can be treated on an outpatient basis.[51,52] Doxycycline has been used mainly for prophylaxis in human beings.[51]

Jarisch-Herxheimer (JH) reaction, fever and hypotension can occur because of the use of penicillins. Toxins released during the leptospira lysis by antibiotics can induce the production and release of cytokines. The appearance of the JH reaction does not contraindicate antibiotic therapy.[53,54]

Intensive care

The severe form of leptospirosis (Weil disease) requires intensive care, mainly regarding renal function, including the possibility of dialysis. Hypotension and hypovolemia are important factors leading to AKI and are present in most patients. Those conditions need to be immediately reverted. Oral hydration is the first choice. In more severe cases, intravenous saline solution should be carefully administered to avoid hypervolemia and pulmonary complications. Patients suspected of having pulmonary hemorrhage should be admitted to the intensive care unit (ICU) and undergo mechanical ventilation at low tidal volumes and high positive end expiratory pressure (PEEP) after recruitment maneuvers.

Renal replacement therapy

Recent studies have shown the benefit of early dialysis in leptospirosis, with a reduction in the mortality rate.[55] In a study carried out in São Paulo, with 33 patients with leptospirosis admitted to an ICU, a significant reduction in mortality was observed in the group undergoing early (on admission) and daily dialysis, as compared with the group receiving late onset dialysis every other day (16.7% vs. 66.7%).[55]

There is no consensus about the best dialysis modality for leptospirosis, and all modalities have already been used, including hemodialysis, peritoneal dialysis, and hemoperfusion.[56] A recent review of cases of leptospirosis associated with AKI in Thailand has shown that therapies such as hemodialysis and hemofiltration, when compared with standard peritoneal dialysis, associate with lower mortality, shorter time of recovery, and a faster reduction in the serum levels of bilirubin, urea, and creatinine.[57]

Recovery of renal function

In the anicteric form, renal function recovers spontaneously in a few days or one week. Normalization of the urea and creatinine serum levels usually occurs in the second week of the disease concomitantly with the increase in the number of platelets and decrease in bilirubin levels.[2] A prospective study assessing long-term renal function of 35 patients with AKI and leptospirosis has shown that the creatinine clearance, sodium proximal reabsorption, urinary acidification, and proteinuria were normal in the third month after disease, but the urinary concentration remained decreased by the end of follow-up, in the sixth month.[19]

The prognosis of AKI in leptospirosis is usually favorable, unless complicated by multiple organ involvement. Pulmonary complications, hyperbilirubinemia, oliguria-anuria, diarrhea, hyperkalemia, advanced age, and associated infection or underlying diseases worsen the prognosis, with mortality ranging from 12% to 36%.[10,58-60]

Mortality

A review of studies in different countries (Brazil, Thailand, Turkey, and French Antilles), using logistic regression to identify the prognostic factors for death in leptospirosis, has shown mortality between 15% and 18%.[61-63] Death is uncommon in the forms of leptospirosis without AKI. Independent factors were related mainly to pulmonary and renal complications. Other factors, such as altered mental status, white blood cell count, thrombocytopenia, and electrocardiographic abnormalities have also been associated with higher mortality.[61-63] Age has not been reported as an independent prognostic factor. In Brazil, the analysis of 42 patients with pulmonary hemorrhage, 66% of whom having AKI, has revealed a mortality rate of 55%. A retrospective study carried out in Brazil with 110 patients with leptospirosis reported the following risk factors for death: oliguria, cardiac arrhythmia, dyspnea, and pulmonary impairment.[10]

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