Pathophysiology of Leptospirosis

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Abstract

Leptospirosis is an acute septicemic illness that affects humans in all parts of the world. Approximately 10% of patients with leptospirosis develop severe disease, the Weil’ syndrome, with ictericia, acute kidney injury (AKI) and pulmonary hemorrhage. Leptospirosis-induced AKI is typically nonoliguric with a high frequency of hypokalemia. Experimental and clinical studies demonstrated that tubular function alterations precede a drop in the glomerular filtration rate and are mainly in the proximal tubule. Studies in humans and animals have demonstrated a decrease in the expression of proximal sodium (NHE3) and water tubular transporter, aquaporin 1 (AQP1) together with higher renal expression of the Na-K-2Cl cotransporter NKCC2. In an experimental model, at the initial phase of the disease the expression of AQP2, the water transport of the collecting duct is decreased, which explains the higher incidence of nonoliguric AKI. During the recovery phase of AKI, AQP2 expression increased in human and animals as a compensatory mechanism. Alveolar hemorrhage, pulmonary edema, ARDS, or a combination of these features may accompanied AKI and is associated with high mortality. Studies with hamsters demonstrated that in leptospirosis, a noncardiogenic pulmonary edema occurs consequently to a decrease in the clearance of alveolar fluid, due to a decrease in sodium transporter in the luminal membrane (ENaC) and an increase in the NKCC1 basolateral membrane transporter. Antibiotic treatment is efficient in the early and late/severe phases and revert all kidney transporters. Early and daily hemodialysis, low daily net fluid intake and lung-protective strategies are recommended for critically ill leptospirosis patients.

Keywords: Leptospirosis, acute kidney injury, acute lung injury, kidney transporters, lung transporters
Leptospirosis is caused by a microorganism of the genus *Leptospira*. There are two species of *Leptospira*. The *L. interrogans* is pathogenic; and the other is nonpathogenic and saprophytic: *L. biflexa*. The *L. interrogans* complex comprises 23 serogroups and approximately 210 serovars (1-3).

Humans acquired leptospirosis by direct contact with blood, tissues, organs or urine of infected animals, or through indirect contact when injured mucosa or skin comes into contact with contaminated water.

The transmission of this disease increases during raining season, when water accumulates during flooding. A marked increase in the number of cases is related globally. The disease is epidemic in tropical and temperate climates.

Leptospirosis can provoke a broad range of manifestations, from benign infection (characterized by nonspecific symptoms) to Weil’s disease, which is a severe form of the disease that causes jaundice, hemorrhagic events and acute kidney injury (AKI) (4). The disease is a common cause of fever in developing countries and continues to be a lethal infection. The mortality rate among patients with Weil’s disease is over 10% (1).

The clinical manifestations of leptospirosis varies from mild symptoms to a severe disease with ictericia, acute kidney injury and pulmonary hemorrhage. The early phase of leptospirosis manifestations lasts 3 to 7 days, and include fever, headaches, myalgia (especially in calves), nausea, vomiting, malaise, and conjunctival hyperemia. Eighty to 90% of patients are symptom free after this initial phase. In this phase, it is possible to isolate leptospires from blood samples. Only 10% progress to the second phase, the Weil’s syndrome. This phase lasts from 4 to 30 days,
and more severe symptoms, such as ictericia, meningitis, pulmonary hemorrhage, acute kidney injury can occur. Immunoglobulin M antibodies are commonly found in this phase.

Weil’s disease provokes potentially fatal hemorrhagic manifestations. Patients can develop significant hemodynamic abnormalities, secondary to the hypovolemia caused by dehydration and the direct effects of leptospiral toxins that damage the vascular endothelium and increase permeability. Hemorrhagic manifestations include ocular suffusion, petechiae, pulmonary hemorrhage, gastrointestinal hemorrhage and hematuria. Thrombocytopenia is seen in more than 70% of cases. Hemorrhage has become recognized as the most serious manifestation of human leptospirosis, and reports of such hemorrhage are increasing worldwide (5). The principal finding involving the central nervous system is headache of sudden onset (in the initial phase). Meningitis is a common complication in the immune phase.

Renal Involvement

The reported incidence of AKI in severe leptospirosis varies from 40% to 60%. The kidney is one of the principal target organs of Leptospira. Leukocytes, as well as, to a lesser extent, erythrocytes, are seen in the urinary sediment of leptospirosis patients. Urinary protein excretion, when present, is typically less than 1 g/day. Bile pigments and granular casts can also be seen. Under dark-field illumination, leptospires can be seen in urine between weeks 1 and 4 of infection (4).

Interstitial nephritis is the mainly pathological alteration in patients with leptospirosis even in those without AKI or tubular necrosis. The infiltration is mainly due to mononuclear cells. Immunohistochemistry demonstrated intact leptospires throughout the tubular basement membrane, among tubular cells, within the tubular lumens, within the interstitium, and, in some
cases and in limited numbers, within glomeruli. Fragments of spirochetes have been found within histiocytes, in the interstitium and in tubules. Glomeruli maintain a normal aspect (6).

Leptospirosis-induced AKI is typically nonoliguric and often includes hypokalemia. Seguro et al. studied 56 patients with leptospirosis- AKI and found a higher frequency of nonoliguric renal failure (7). The authors also found that morbidity and mortality were lower in those with nonoliguric AKI than in those with oliguric AKI. The time to reach a serum creatinine level of 1.5 mg/dL, a parameter of recovery from AKI was shorter in nonoliguric patients. Nonoliguric patients required dialysis less frequently than oliguric patients.

Interesting observation was that of the 30 oliguric patients at the 1st day of hospitalization, 16 became nonoliguric at 2nd day after volume expansion (if not with pulmonary edema) and furosemide administration, none of these nonoliguric patients died, while 50% of the remaining oliguric died, mainly from pulmonary involvement.

An interesting finding was that 45% of the patients were hypokalemic (K<3.5 mEq/L) on the first day of hospitalization, and none were hyperkalemic.

In order to explain a possible mechanism to the high frequency of hypokalemia, 11 of these 56 patients were studied prospectively by measuring fractional excretion (FE) of sodium and potassium on the 1st and 8th days of hospitalization. The urinary K/Na ratio was also calculated. Since practically all K filtered by the kidneys is reabsorbed in proximal tubule and in the thick ascending limb of Henle, the urinary K is due to secretion of this ion in distal and cortical collecting tubules, consequently to lumen negative potential generated by Na reabsorption, the urinary K/Na ratio is considered an indirect evaluation of distal segments function.
The data showed that mean serum creatinine decreased from 6.0 mg/dL to 1.6 mg/dL and serum K increased from 3.5 to 4.3 mEq/L. The mean FENa (normal value 1%) was elevated on the 1st day (6.0%) and decreased to 1.2%, while FEK (normal value 8-12%) decreased from 102.5% to 12% and the mean urinary K/Na ratio decreased from 0.62 to 0.34. The elevated FEK which fell concomitantly with the FENa and urinary K/Na ratio suggests that the initially increased distal K secretion is secondary to an increase in the delivery of Na to distal segments consequently to a decrease in NaCl reabsorption in the proximal tubule and the elevated urinary K/Na ratio on the 1st day suggests that the distal segments are preserved in leptospirosis.

In an experimental study with guinea pigs inoculated with *Leptospira icterohaemorrhagiae*, Magaldi et al evaluated the renal tubular function, using clearance and microperfusion of isolated nephron segments (8). All animals with leptospirosis presented jaundice, inulin clearances were normal. Animals with leptospirosis presented higher FEK than did normal animals. High doses of furosemide were used in order to block sodium chloride reabsorption in the thick ascending limb of Henle’s loop of the leptospirosis-infected animals, which subsequently presented FENa and FEK that were higher than those seen in normal animals treated with the same diuretic dose. In the infected, furosemide-treated animals, mean FEK increased from 26% to 136%, confirming that the distal tubular segments were intact, and that distal potassium secretion had increased.

The microperfusion studies performed in this study showed that the medullary thick ascending limb of normal animals presented transepithelial potential difference and relative sodium-chloride permeability identical to those seen in that of leptospirosis-infected animals, indicating that this nephron segment was functioning normally. In the inner medullary collecting duct of animals with leptospirosis, osmotic water permeability, diffusional water permeability and urea permeability did not increase in the presence of vasopressin, indicating vasopressin resistance in the inner medullary collecting duct (8).
This study demonstrated that tubular function alterations in leptospirosis precedes the fall of glomerular filtration rate, which could explain the high frequency of hypokalemia in leptospirosis-induced AKI even in oliguric patients.

The hypokalemia is a marker of less kidney dysfunction in patients with leptospirosis and AKI. In a prospective study of 42 patients with acute lung injury in leptospirosis, most of them with AKI, a serum potassium level > 4 mEq/L was independently associated with mortality. Lower potassium levels were observed in survivors, suggesting that there is less renal dysfunction in this group. The higher potassium levels observed in nonsurvivors might have been provoked by more severe renal dysfunction or rhabdomyolysis. The association between creatinine phosphokinase levels and maximum serum creatinine levels in these patients suggests that rhabdomyolysis contributes to AKI and higher potassium levels in nonsurvivors (9).

In hamsters infected with Leptospira Pomona, Andrade et al. studied sodium transporters in the kidney and lung (10). The infected hamsters presented elevated levels of creatine phosphokinase and total bilirubin and a lower creatinine clearance than control animals, indicating that they developed AKI. Urine output and fractional excretion of sodium and potassium were increased in animals with leptospirosis when compared with controls, similar to the human disease. Immunoblotting was used to determine the expression and abundance of water and sodium transporters. A significant decrease in the protein expression of the sodium/hydrogen exchanger isoform 3 (NHE3), which is expressed in the apical membrane of the proximal tubule was observed in infected animals, and can partially explain the polyuria and might completely explain the high FENa. A marked increase in Na-K-2Cl cotransporter of the thick ascending limb of Henle (NKCC2) observed in the infected animals represents a compensatory response to the greater sodium chloride and water delivery to this tubular segment. The protein expressions of
the NaCl transporter of the distal tu lue (NCC) and of the collecting duct (α-ENaC) were unchanged in leptospirosis-infected hamster and indicates an integrity of these two distal segments. The downregulation of the expression of aquaporin-2 may also contribute the polyuria observed in leptospirosis animals.

Araujo et al performed immunohistochemistry in kidneys removed during autopsies of human leptospirosis cases and kidneys of autopsy of human non-leptospirosis cases with and without evidence of acute tubular necrosis. A decrease in the expression of NHE3, AQPI (the water channel) and α-Na-K-ATPase was observed in proximal convoluted tubule cells of leptospirosis patients while the expression of NKCC2 cotransporter was preserved in leptospirotic kidneys. This study confirmed the findings observed in experimental models indicating that the primary injury in leptospirosis is in the proximal convoluted tubules.

Other tubular dysfunctions have been reported. Khositseth et al. studied 20 leptospirosis patients and found that 50% had hypomagnesemia during hospitalization and 75% had elevated Mg urinary excretion. Phosphate wasting occurred in 10 patients (50%) due probably to a dysregulation in the tubular reabsorption of phosphate. Both disturbances improved in 2 weeks after admission. Urinary excretion of N-acetylglutamate and β2-microglobulin was increased in all 20 patients indicating a proximal tubular dysfunction (12).

Other study showed that hypomagnesemia occurs mainly in the recovery phase due to a decrease in tubular reabsorption of Mg (13). Sanches et al studied 54 leptospirosis patients with AKI during the recovery phase when mean values of serum creatinine was 1.9 mg/dL, 24-h urinary volume 5437 mL, FENa (4.5%), FEK (23.5%), FE Mg (33%, normal 2-4%).
In the same study, the NKCC2 and AQP2 urinary exosome excretion analyzed by western blot in 6 of these leptospirosis patients was significantly higher than those of 4 healthy control patients. Indicating that in the recovery phase the marked increased in NKCC2 expression as well AQP2 expression might represent a compensatory effect, and that the increase in Mg excretion may be due to a decrease in Mg reabsorption in the proximal tubule and distal tubule, not in the thick ascending limb of Henle (13).

Increased knowledge of leptospirosis-induced electrolyte disorders and polyuria is of immediate clinical significance, since early diagnosis and correction of these electrolyte disorders can improve clinical outcomes for these critically ill patients.

The role of innate immune responses in protection against and pathogenesis of severe leptospirosis remains unclear. Toll-like receptors (TLRs) are now recognized as the major receptors for microbial pathogens on cells of the innate immune system. In sepsis organ-induced dysfunction, especially in the kidneys are due to alterations in the innate immune receptors, inflammasome components and proinflammatory cytokines (14). Viriyakosol et al. demonstrated that intact TLR4 signaling contributes to the control of the tissue burden of Leptospira in nonlethal leptospiral infection (15). Natural mammalian reservoir hosts of leptospires generally do not develop severe pathology in leptospiral infection. TLR4-deficient mice when infected with Leptospira interrogans serovar Icterohaemorrhagiae died from jaundice and pulmonary hemorrhage similar to patients.

It has been well documented that leptospires can persist for prolonged periods of time in the renal tubules of a wide variety of mammals. Therefore, the fact that the authors found significantly higher numbers of leptospires in TLR4-deficient mice, particularly in the target
organs mediating leptospiral disease (liver, lung, and kidney) and transmission (kidney), is novel and important.

In order to elucidate the role of leptospira outer membrane proteins in tubular nephritis, an outer protein membrane from a pathogenic leptospira, *Leptospira shemani* (32-kDa lipoprotein, LilL32.) was administered to culture of mouse proximal tubule cells, resulting in a dose-dependent stimulatory increase in monocyte chemoattractant protein-1, nitric oxide synthase (iNOS), RANTES and TNFα, resulting an increase in nuclear binding of NK-kappa B in proximal tubule cells. These data demonstrated that LipL32 is involved in the pathogenesis of tubulointerstitial nephritis of leptospirosis (16).

**Acute Kidney Injury in Children with Leptospirosis**

Leptospirosis is diagnosed less frequently in children than might be expected based on the level of exposure to hazards. This might be attributable to a failure to consider the diagnosis or differences in the manifestations of leptospirosis in children. Marotto et al. studied 43 leptospirosis-infected children from 4 to 14 years of age (17). The authors observed AKI in 79%, and, as in adults, the AKI was primarily nonoliguric. Eleven of the children had hypokalemia at admission. Only 2 children required dialysis during hospitalization. When compared with adult populations, children with leptospirosis-induced AKI presented better outcomes. There was only one death among the children studied.

An interesting case of anicteric leptospirosis-induced AKI and meningitis was described in a 19-month-old child whose family lived in an area that had been flooded one week prior to the onset of symptoms. Reversal of the AKI was obtained after antibiotic treatment and intravenous fluid
therapy. This case report should alert pediatricians to the potential of leptospirosis in children with AKI and meningitis, particularly in endemic areas (18).

More recently, Spichler et al in a prospective study compared the evolution of severe leptospirosis in pediatric and adult populations. Children had lower rates of jaundice, oliguria and creatinine levels, besides that they had also less pulmonary involvement and thrombocytopenia. The mortality rate was 5% in children and 27% in adults (19).

**Pulmonary Manifestations in Leptospirosis**

Pulmonary edema/hemorrhage leading to ARDS constitutes the most severe manifestation of lung injury in leptospirosis.

The ability of the lungs to resolve edema is crucial for restoring lung function and is known to be impaired to patients with ARDS (20). A strong association between AKI and ARDS has been consistently demonstrated. It has also been shown that respiratory and renal failures are independently associated with mortality. Weil’s disease manifests as severe lung injury (diffusive alveolar hemorrhage, pulmonary edema, ARDS, or a combination of these features) accompanied by AKI and can be therefore highly lethal (9).

Worldwide reports of pulmonary manifestations in leptospirosis have been increasing in recent years. Pulmonary involvement in leptospirosis ranges from 20% to 70% (1-2). In 2006, in the Metropolitan area of São Paulo - Brazil, the frequency of Weil’s disease with pulmonary hemorrhage was 69% (21).
Leptospirosis-associated hemorrhagic pneumonitis can manifest as cough, dyspnea and hemoptysis, accompanied by radiological abnormalities that range from focal interstitial infiltrate to diffuse alveolar infiltrate. More severe respiratory symptoms, such as respiratory failure due to pulmonary hemorrhage, can be seen, resulting in high mortality rates (1-2).

Early identification of leptospirosis-associated hemorrhage syndrome is very important for earlier management and reduction of mortality. Recently, Marotto et al developed a multivariate model for predicting leptospirosis-associated pulmonary hemorrhage syndrome in a prospective study of 203 patients admitted with severe leptospirosis at the Intensive Care Unit of the Emilio Ribas Institute of Infectology (São Paulo, Brazil) (22).

Leptospirosis is now recognized as a major cause of severe pulmonary hemorrhage syndrome. Acute respiratory distress syndrome (ARDS), which is a prominent feature of this manifestation, can also occur in the absence of documented bleeding. Pulmonary hemorrhage is one of the major causes of death in leptospirosis.

In animal studies, Spichler et al. showed that leptospires appear to prefer organs such as the kidney or liver, over the lungs (23). A morphologic study, under light microscopy of the lungs of leptospirosis patients revealed edema of the intra-alveolar septa (24). Mild to moderate inflammatory infiltrate was found, with a predominance of macrophages, amid lymphocytes and plasmocytes. In addition, endothelial tumefaction was seen, and some patients presented alveolar hemorrhage. Leptospiral antigen was also detected as positive granular material on the luminal surface of the endothelium and in the cytoplasm of the endothelial cells of septal capillaries, as well as, in the filamentous form, attached to the endothelium of the septal capillaries.

In another animal study, Nally et al. used immunofluorescence staining to show that deposition of immunoglobulin can be granular (classical immune deposits as seen in certain renal diseases),
or linear (as occurs in other renal diseases and Goodpasture’s syndrome). Granular deposits are visible using immunofluorescence, electron microscopy and sometimes even light microscopy. Linear deposits are seen through immunofluorescence, although not typically under electron microscopy. The pathogenesis of the lung disease in this experimental system best fits with a model of linear deposition of immunoglobulin and complement as occurs in Goodpasture’s syndrome or anti-glomerular basement membrane disease. The inflammatory infiltrate of monocytes and polymorphonuclear cells observed in thickened alveolar septa included some cells in which leptospiral antigen was demonstrated using immunohistochemistry. There are several possibilities to explain the presence of inflammatory cells observed in the alveolar septum: antigenic leptospiral debris found within the alveolar septum might reflect the clearance of intact spirochetes by inflammatory cells; endothelial damage evidenced by the blebbing formation of endothelial cells seen under electron microscopy might have drawn an inflammatory response; or, finally, complement activation evidenced by the detection of C3 might have caused the inflammation (25).

As we can see in Figure 1, in alveolar cells (pneumocyte), the active transport of sodium to the interstitium by the α-Na-K-ATPase pump generates an osmotic driving force favorable to the entrance of sodium from the alveolar lumen to pneumocyte via α-ENaC. The osmotic gradient between the lumen and the interstitial space promotes the movement of water via the paracellular pathway. Water also crosses the cell via a water channel (AQP5). Cellular volume is regulated primarily by electroneutral cotransporter NKCC1, which is found in virtually all cells and mediates coupled influx of sodium, potassium and chloride.

Andrade et al. showed that leptospirosis infection decreases α-ENaC protein expression in lung membranes of hamsters infected with leptospirosis (10). The authors also found that basolateral protein expression of the Na-K-2Cl cotransporter NKCC1 was upregulated, as well as that
aquaporin 5 and α-Na-K-ATPase protein expression were unchanged, in the lung tissue of hamsters infected with leptospirosis.

The decrease in ENaC and the increase of NKCC1 dissipates the osmotic gradient of sodium between alveolar lumen and interstitium leading to a decrease in water reabsorption in the intercellular space leading to pulmonary edema (Figure 2).

In human patients, leptospirosis has many presentations, including the severe pulmonary form (ARDS), which is characterized by impairment of the alveolar-capillary barrier. Impaired pulmonary fluid clearance resulting from downregulated α-ENaC expression, as well as the potential derangements related to increased NKCC1 expression, might have significant deleterious effects in the context of increased pulmonary permeability such as that observed in ARDS.

Similar findings are observed in sepsis, a common cause of AKI and acute lung injury (ALI). Rats submitted to cecal ligation and puncture (CLP), a model of sepsis, developed AKI and ALI, with pulmonary edema, downregulation of α-ENaC expression and upregulation of NKCC1 (26). These findings explain that although a positive water balance is considered a major predictor of outcome in patients with sepsis, pulmonary edema can occur even when the water balance is normal or negative. Rabb et al. showed that, in rats without lung injury and submitted to bilateral nephrectomy, there is a decrease in sodium cotransporter expression, followed by increases in vascular permeability and interstitial edema, providing evidence of the crosstalk between the lungs and kidneys (27).

Oxidative stress plays an important role in AKI and ALI related to sepsis. Campos et al demonstrated that the administration of the antioxidant, N-acetylcysteine, 2 days before CLP
ameliorates AKI, decreases pulmonary edema by α-ENaC upregulation and NKCC1 downregulation associated with a decrease in oxidative stress markers (plasma thiobarbituric acid reactive substances and 8-isoprostanate in lung and kidney tissue) (26). Future studies are needed to verify the beneficial effect of NAC in animal model of severe leptospirosis.

Experimental studies demonstrated that glucocorticoids also increases α-ENaC expression in lung and may be an additional therapy to leptospirosis acute lung injury (28). Clinical studies are controversial and until this moment there is no consensus about the use of glucocorticoids in leptospirosis patients with pulmonary involvement.

Furosemide inhibits NKCC1 and may contribute to control ALI in leptospirosis. It is possible that the findings observed by Seguro et al that treatment of initially oliguric leptospirosis patients with furosemide besides increase diuresis in half of these patients which became nonoliguric may increase clearance of alveolar fluid by the inhibitory effect on pneumocyte NKCC1 (7). Measurement of the clearance of alveolar fluid in leptospirosis patients with oliguric AKI and ALI before and after furosemide administration are necessary to prove this hypothesis.

Cardiovascular Manifestations

Cardiac arrhythmias occur in leptospirosis, atrial fibrillation is the most common; atrioventricular blockage may also be observed. Myocarditis, pericardium rub and effusion can also occur. De Brito et al., in autopsies of 20 patients who died from leptospirosis (29), observed interstitial edema, myocardial infiltration, acute coronary arteritis and aortitis, leptospiral antigens were detected in the aorta and coronary arteries in these cases.
Marotto et al (9) measured the initial hemodynamic profile in 12 patients with severe leptospirosis and observed a high cardiac index (4.71 ± 1.41 L/min/m²); normal pulmonary capillary wedge pressure (10 ± 5 mmHg); and low mean systemic vascular resistance (1393 ± 882 dyne/s/cm²). This hemodynamic profile is similar to the observed in patients with sepsis.

The mortality of patients with leptospirosis and ARDS (on mechanical ventilation) and AKI (on dialysis) in the Intensive Care Unit of the Emílio Ribas Institute of Infectology, was 55% from 1994 to 1997 and 43% from 1998 to 2001 (30).

Recent evidence suggests that dialysis dosage affects outcomes in critically ill patients with sepsis-induced AKI. Andrade et al evaluated the effects of dialysis dosage in the severe form of the Weil’s disease: patients with leptospirosis and ARDS (on mechanical ventilation) and AKI (on dialysis) (30). They found that the prompt initiation of dialysis, together with daily dialysis sessions, reduced the mortality to 16.7%, compared with 66.7% among the patients who performed hemodialysis on alternate days. Based on these results, they concluded that early and daily dialysis is more appropriate for critically ill patients with Weil’s disease.

The ARDS Clinical Trials Network study showed that a conservative fluid management protocol aimed at achieving lower central venous pressure or lower pulmonary artery occlusion pressure resulted in a greater reduction in the net intake without an increase in adverse events, as compared with a liberal fluid management protocol aimed at achieving higher intravascular volume and cardiac filling pressures (31). The conservative strategy improved lung function, shortening the duration of mechanical ventilation and ICU stay without increasing nonpulmonary organ failure. These results lend credence to the idea that a conservative strategy of fluid management should be used in patients with acute lung injury.
During mechanical ventilation, it is also recommended that lung-protective strategies based on low tidal volumes (6 mL/kg) be used in order to guarantee lower plateau pressures. High positive end-expiratory pressures after recruitment maneuvers, used in order to ensure alveolar stabilization and recovery of gas exchange, have been associated with decreased mortality in this critical condition.

**Treatment**

Antibiotic treatment is efficient in the early and late/severe phases of the disease. A recent study in leptospirosis-infected hamsters showed by immunohistochemistry that infected animals presented high amounts of detectable leptospiral antigens in kidney, lung and liver tissues, and that the expression of NHE3 and NKCC2 is decreased in the kidney. Early and late ampicillin treatment was associated with minimal or no detection of leptospiral antigens and rescue the expression of NHE3 and NKCC2 (23).

Severe leptospirosis is treated with intravenous penicillin (1,500,000 U every 6 h). Intravenous ceftriaxone (1 g once daily) or cefotaxime (1 g every 6 h) have equivalent efficacy as penicillin. Treatment must be maintained for 7 days. Although Jarisch-Herxheimer reactions during initiation of an antibiotic can occur, they are less common in leptospirosis than in other spirochetal infections. Azithromycin and Doxycycline have been found to be effective in the treatment of leptospirosis in patients who were ambulatory and did not present involvement of vital organs (2).
Future Perspectives

The complete genome of *L. interrogans* serovar *Lai*, strain 56601, and *L. interrogans* serovar *copenhageni*, strain Fiocruz L1-130 were sequenced in China and Brazil respectively. The genome of *Leptospira* consists of two circular chromosomes and is highly conserved between the two serovars (32, 33). The sequencing of these genomes may contribute to development of specific culture media, identification of antibiotic resistance mechanisms, identification of virulence factors, and clarification of host-pathogen interactions’ mechanisms, as well as the development of monoclonal antibodies and vaccines.

Weil’s disease is a classic model of sepsis. Patients with Weil’s disease typically develop severe lung injury (diffuse alveolar hemorrhage, pulmonary edema, ARDS or a combination of these features) accompanied by AKI. Despite improved strategies for supporting vital organs and resuscitating patients, the incidence and mortality rates of septic patients remain quite high. The prevention of multi organ dysfunction related to sepsis in intensive care settings continues to represent a great challenge.

Recently, there are studies, mainly in CLP animal model to determine whether drugs which are able to reducing apoptosis, oxidative stress, lipid peroxidation, and also promoting renal tubular cell regeneration, vascular regeneration, and neoangiogenesis could prevent the multi organ dysfunction seen in the CLP model of sepsis. These drugs are also being tested whether they could be used as therapeutic agent after the induction of the CLP sepsis.

Erythropoietin (EPO) has emerged as a major tissue-protective cytokine in the setting of stress. Souza et al (34) investigated the role of EPO in sepsis-related acute kidney injury using a CLP model. At post-CLP-procedure hour 24, septic rats which received EPO presented significantly higher inulin clearance (gold standard to measure renal function) than did CLP rats. In renal
tissue, pre-CLP EPO administration prevented the sepsis-induced increase in macrophage infiltration, as well as preserving eNOS expression, EPO receptor expression, IKK-α activation, NF-κB activation, and inflammatory cytokine levels, thereby increasing survival. They concluded that this protection, which appears to be dependent on EPO receptor expression activation and on eNOS expression, is attributable, in part, to inhibition of the inflammatory response via NF-κB downregulation (34).

Continuous erythropoietin receptor activator (CERA) is an erythropoietin with a unique pharmacologic profile and long half-life. Rodrigues et al (35) hypothesized that pretreatment with CERA would be renoprotective in the CLP model of sepsis-induced AKI. They found that pretreatment with CERA preserved renal and tubular function, as well as the expression of NKCC2 and AQP2. In addition, CERA maintained plasma lactate at normal levels, as well as preserving plasma levels of transaminases and lactate dehydrogenase. Renal expression of TLR4 and NF-κB was lower in CLP rats which received CERA than in CLP rats, as were CD68-positive cell counts, whereas renal EpoR expression was higher. Plasma levels of all measured cytokines were lower in CLP+CERA rats than in CLP rats (35).

The question is whether these new therapies could be in some way effective in the Weil syndrome.
References


**Figure Legends**

**Figure 1:** Active transport by the Na-K-ATPase pump generates an osmotic driving force that favors the entrance of sodium via α-ENaC. There is therefore continuous transport of sodium from the lumen into the interstitium. The osmotic gradient between the lumen and the interstitium promotes the movement of water via the paracellular pathway. The cotransporter in the basolateral membrane, NKCC1, regulates cellular volume (10).

**Figure 2:** In leptospirosis the α-ENaC protein is downregulated leading to a decreased influx of sodium from the lumen into the cells. The upregulation of NKCC1 increases the influx of sodium from the interstitium into the cells. Both mechanisms decreases the net flux of sodium from alveolar lumen to interstitium, decreased the osmotic gradient and decrease water flow through paracellular pathway causing accumulation of water in the lumen (10).
Figure 1

![Diagram of Pneumocyte showing transport proteins and ion concentrations.](image)
Figure 2