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Narrative review of generalities of the genus *Leptospira* and its virulence factors associated with renal pathophysiology

Revisión narrativa de generalidades del género Leptospira *y factores de virulencia asociados a la fisiopatología renal*

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ABSTRACT. Worldwide, leptospirosis is the most highly prevalent zoonosis. Although the wide range of clinical manifestations of leptospirosis in humans is well-documented, knowledge of the mechanisms through which this pathogen causes kidney disease remains limited. This narrative review of the scientific literature presents experimental studies of pathophysiology and kidney disease in leptospirosis, both in humans and animals, and the results show that virulence factors are involved in kidney damage by inducing interstitial tubular nephritis, which is the most frequent pathological manifestation, additionally, to the acute non-oliguric renal lesion with hypokalemia, and loss of magnesium and sodium. Finally, it is concluded that in leptospirosis, the initial lesion in the kidney is caused by damage to the cell membrane of the proximal tubular region cells by pathogenic *Leptospira* virulence factors, thus exacerbating the immune response.

Keywords: Kidney failure, *Leptospira*, Leptospirosis, Pathogenesis, Virulence factors.

INTRODUCTION

Leptospirosis is a re-emerging infectious disease and one of the main zoonotic causes of morbidity and mortality affecting animals and humans worldwide.[1–3] It is estimated that it affects approximately 1.03 million people each year.[4-6] This disease is caused by pathogenic bacteria belonging to the genus *Leptospira*, as well as the *Leptospiraceae* family and Spirochaetales order.[7-9] Leptospirosis is characterized as a febrile, biphasic, usually anicteric disease, but which can result in liver failure and acute kidney injury; the latter being the most common cause of death.[10,11]

The methodology used in this narrative review was the search for articles from October 2009 to July 2022 in three international databases: Medline (via PubMed), Scopus, and Science Direct. We used a combination of the following search terms: [Leptospir* AND (phylogenetic OR virulence OR genomic OR pathophysiology OR renal OR kidney)]. This review aims to describe recent advances related to virulence factors, the molecular mechanisms of pathogenic species of the genus *Leptospira*, and the effects on the immune system associated with the renal pathophysiology of leptospirosis.

The etiological agent of leptospirosis

Leptospira organisms are flexible, spiral-shaped, or coile; this mobile, aerobic spirochetes, usually 5-15 µm long with very thin spiral turns of 0.1 to 0.2 µm wide. Often one of the ends

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of this bacterium is hook-shaped. They have very characteristic flagella called axial filaments which are located between the outer cell envelope and the protoplasmic cylinder (periplasmic space). This morphological characteristic allows them to effect a rotational movement that gives the bacteria its spiral forward motion[4,8] (**Figure 1**).

All species of this genus have a cellular envelope analogous to that of gram-negative bacteria, which consists of two membranes, one cytoplasmic and one external. The cytoplasmic body and the axostil are spiral-shaped with an enveloping membrane that surrounds both structures.[12,13] This multi-stratified outer membrane has an abundance of lipids (20%), and the bacterium also contains peptidoglycan. However, it has a notable difference: the peptideglycan layer is associated with the cytoplasmic membrane instead of being associated with the outer membrane, which is unique to the spirochetes, and constitutes a singular characteristic of its evolution[4,5,14–17] (**Figure 1**). Some of these bacteria also contain α, ε-diaminopilemic acid. The outer membrane has very immunogenic lipopolysaccharides (LPS), which are responsible for the specificity of the serovars[18] (**Figure 1**).

All species of the genus *Leptospira* generally have two chromosomes; one called the major chromosome and another called the minor chromosome. All genomes are notably different in size, genomic composition, and the number of genes and proteins expressed. There is also evidence of large-scale genomic rearrangements.[14] Although 65 species have now been described[14,16] distributed as follows: 19 Pathogens, 21 Intermediate pathogens, and 27 Saprophytes (**Figure 2**), only the complete genomes of seven species are known, these being *L. interrogans, L. borgpetersenii, L. mayottensis, L. alstonii, L. kmetyi, L. biflexa* and *L. santarosai* (**Figure 2**).

Leptospirosis causes life-threatening manifestations such as pulmonary hemorrhage syndrome and Weil's syndrome, and has become one of the world's leading causes of hemorrhagic fever and acute kidney injury.[19] Depending on the host and serovar involved, leptospirosis behaves like a syndrome that varies from subclinical manifestations with a self-limiting febrile syndrome in 80 to 90% of the cases to potentially fatal febrile manifestations in 5 to 10% of the cases associated with hemorrhagic tendency,[5] in addition to severe symptoms such as jaundice accompanied by renal and hepatic insufficiency.[4] This particular symptomatology is known as Weil's syndrome, which without adequate treatment can cause death in up to 50% of the cases where early renal damage is very frequent, characterized by tubule interstitial nephritis and tubular dysfunction.[14,15,19]

Leptospira reservoirs include wild and domestic animals, with rats being the main reservoir in urban areas.[10,20] Transmission to humans occurs through direct contact with the blood, tissues, organs, urine of infected animals, or water contaminated with urine from infected rats. The bacterium enters through lacerations in the skin, mucous, or conjunctiva. It then degrades the tissue until it reaches the endothelium. It is then transmitted hematogenously to different organs, such as the liver or lungs, but mainly to the kidney, which is its target organ[21] (**Figures 3,4**).

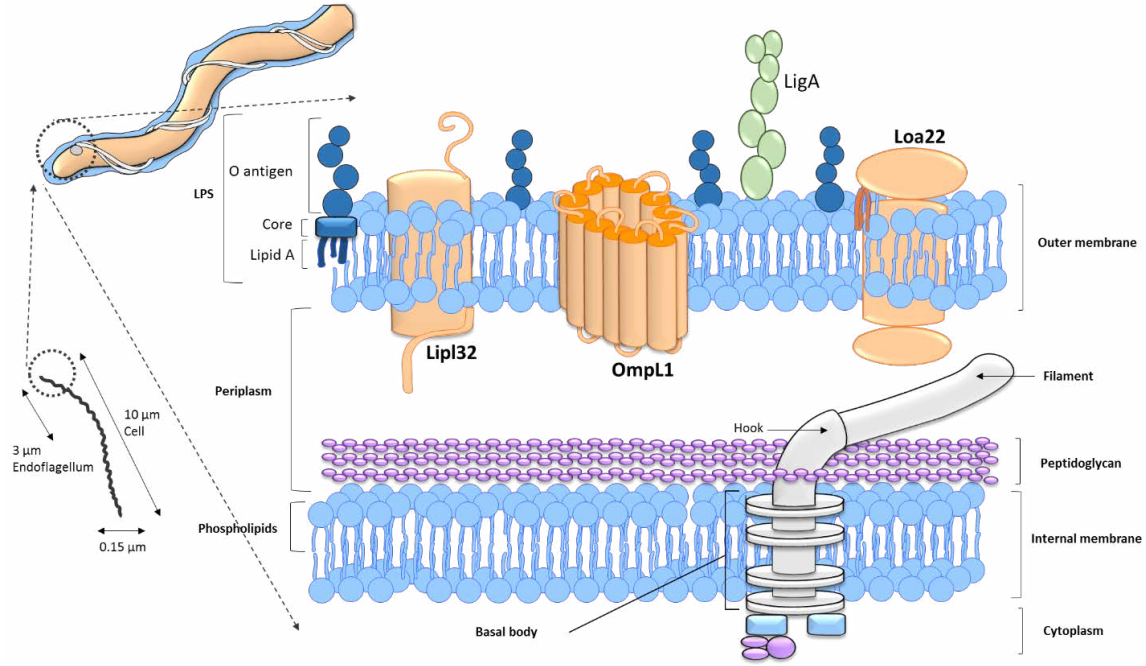

Figure 1. Cellular morphology of *Leptospira* spp. It is a helical bacterium that is 0.15 µm in diameter and 10 µm in diameter. The motility of *Leptospira* depends on the presence of two endophlagels, located at each end of the bacteria, which has a length of 3 µm. This gives it its typical spiral movement. It also shows the cell wall that is composed of an inner membrane, a thin layer of peptideglycan, and an outer membrane that has lipopolysaccharide (LPS) that is exposed on the surface and is composed of core, lipid A and O antigen. The endophage with its hook and basal body is shown. It has a rotating molecular motor that allows the movement of the flagellar filament, which is connected through the hook to the basal body. This enables its characteristic rotation. The Loa22, OmpL1, and LipL32 proteins that are fully or partially exposed are all found in external membranes and generate the first contact with the host cells (Source: prepared by authors).

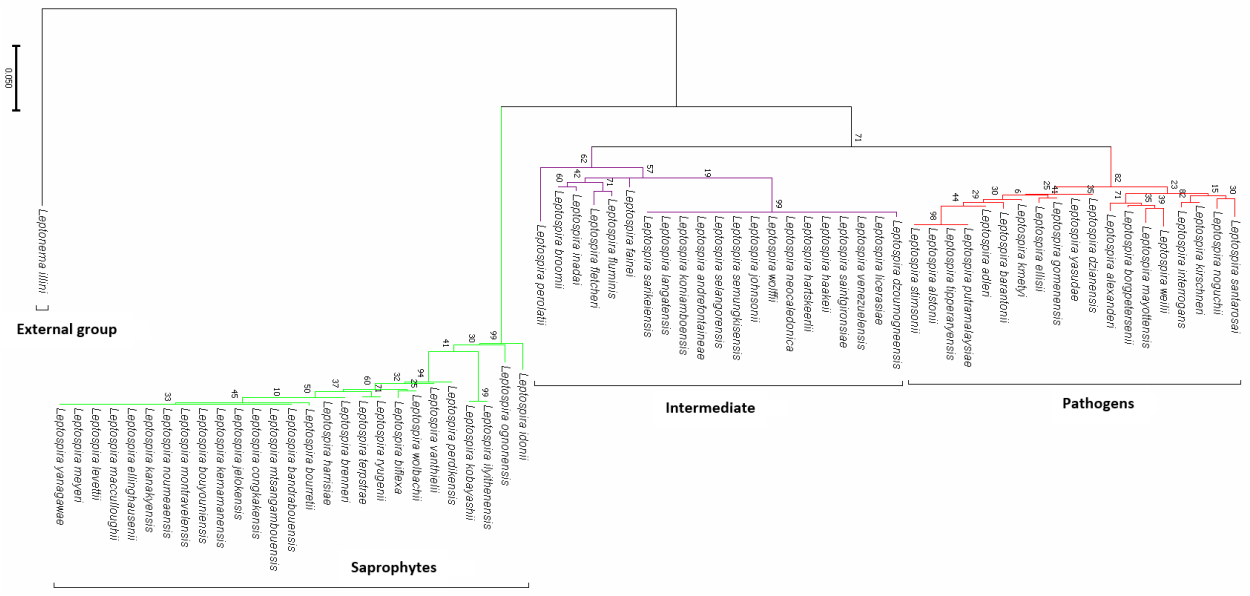

Figure 2. Identification of the 65 species belonging to the genus *Leptospira* by phylogenetic analysis, divided into three groups which are pathogens, intermediate pathogens, and saprophytes, in addition to the external group. Phylogenetic reconstructions for the *16s* ribosomal gene through the MEGA7 program are shown (Source: prepared by authors).

Once it reaches the kidney, a specific mechanism is necessary for *Leptospira* to cross into the lumen of the proximal renal tubules, adhere to the renal epithelial cells, evade the immune response, and acquire the nutrients necessary for survival.[22] This is possible because of its virulence factors[4] (**Figure 4**). Part of the mechanism of renal failure in leptospirosis has not been fully studied, but studies have been conducted in a hamster model where it was shown that after the intraperitoneal inoculation of *Leptospira*, the route of entry is by penetration of the capillary lumen into the kidney[4,14] (**Figure 4**), through the fenestrated endothelium and then to the glomeruli. This occurs approximately after the first two hours post-infection. It then enters the peritubular capillaries, migrating and entering the interstitial tissue where, on days four to eight, it causes edema, infiltrates the cells, and finally remains in the lumen of the proximal contoured tube of the nephron after day ten, causing

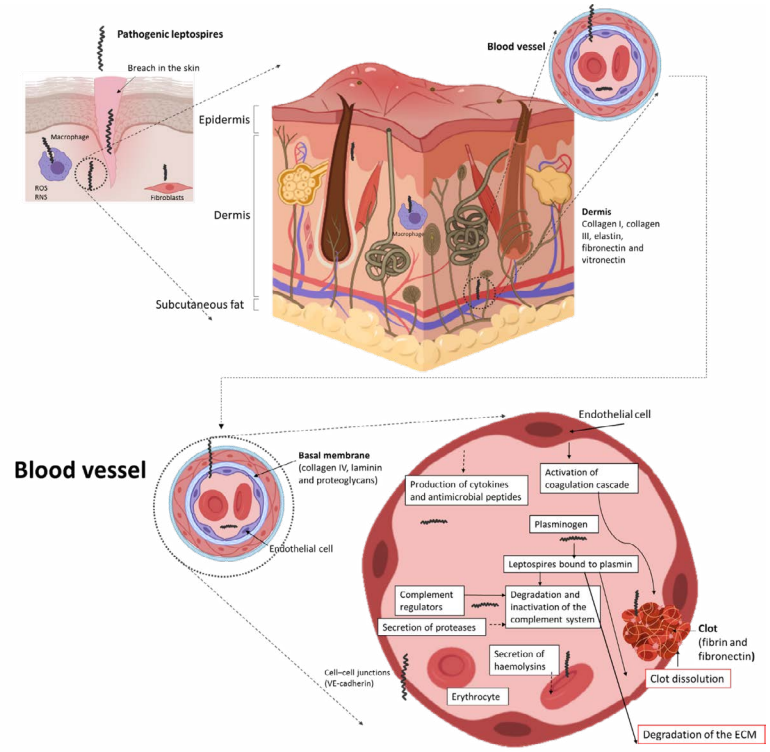

Figure 3. The initial stages of infection by pathogenic leptospires. Pathogenic leptospires enter through lacerated skin or intact oral, nasal, or conjunctival mucosa. They migrate rapidly through the dermis (connective tissue components collagen I, collagen III, fibronectin, vitronectin and elastin) until reaching the endothelium. Once there, they can destroy the endothelium or translocate it and penetrate the endothelial barrier of the blood vessels to reach the blood. Endothelial cells are activated after aggression or detection of leptospires. Due to this, and the detection of antimicrobial peptides, an inflammatory response is initiated where cytokines and leukocytes are involved. However, pathogenic spirochetes have the ability to evade the immune response through components that bind and regulate the complement system. Many innate immune system cells, such as macrophages, can detect and phagocytize leptospires and release reactive oxygen species (ROS) and reactive nitrogen species (RNS). However, the bacteria can also sometimes survive and replicate within macrophages and be released by apoptosis. They also have proteases that help to degrade tissue or platelet clot, facilitating microhemorrhage in the tissues to acquire nutrients and hematogenous spread towards several organs, and are able to reach organs such as the lungs, liver, spleen, muscles, and kidneys, among other organs. After several weeks, the bacteria can be eliminated from the blood and most of the organs, except for the kidney (the most important organ in leptospirosis) where the spirochete lodges, persists and colonizes. The bacteria are secreted for months in the urine, generating renal complications that can be fatal (Source: prepared by authors).

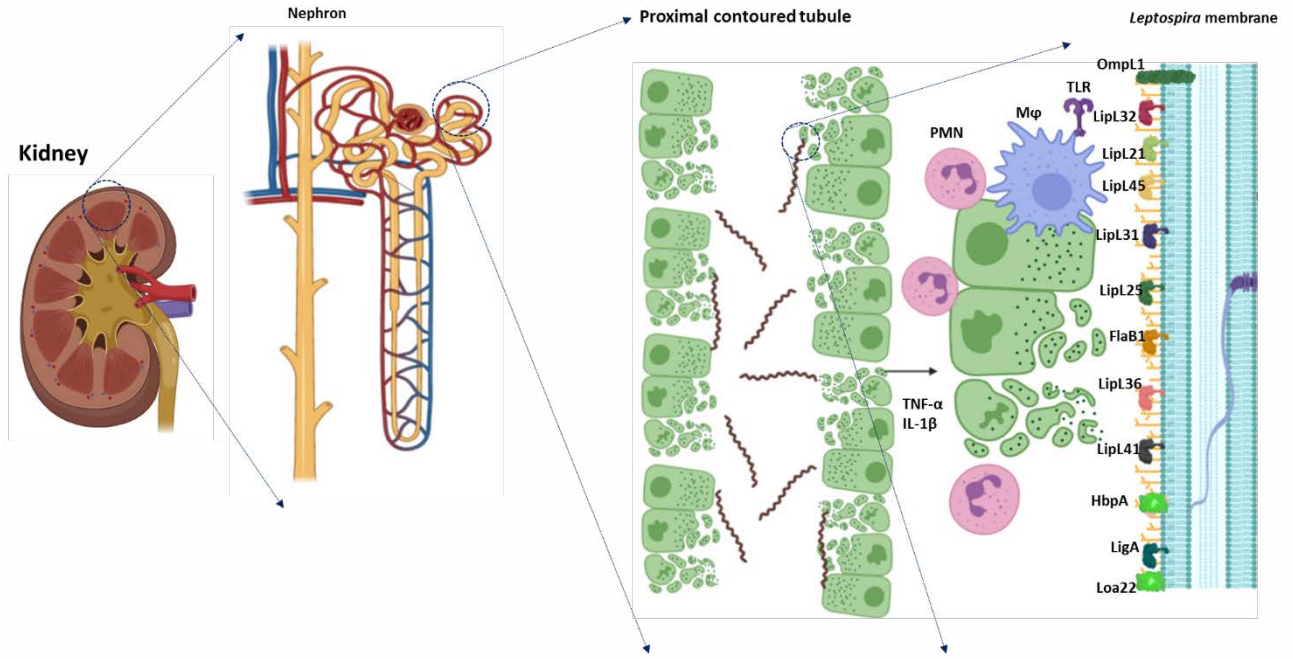

Figure 4. Interstitial tubule nephritis. The graph shows a cross-section of the kidney. Note that the zoomed portions are added for presentation purposes, like in the proximal contoured tube where the membrane-bound leptospires are frequently found, as well as the bacterium where the increased bacterial membrane is observed, and where the main factors of virulence of the spirochete are observed. It also represents the main cells of the immune system. The lesion commonly occurs from direct damage by the bacteria through virulence factors and the exacerbation of immune response to the tissue causing interstitial tubule nephritis, and ultimately tubular necrosis (Source: prepared by authors).

interstitial nephritis and being associated with microvascular lesions, especially in the corticomedullary area.[16,23] Nonoliguric acute renal damage (AKI, acute kidney injury), with or without normokalemia, is frequent in cases of leptospirosis, and if it is accompanied by an increase in blood potassium levels, its presentation is more severe.[22,24] This narrative review presents the association of kidney disease with some virulence factors that have been reported as more relevant in leptospirosis (**Figure 4**).

Immune response and virulence factors associated with renal damage by *Leptospira*

In *Leptospira*, the outer membrane is made up of antigenic components and virulence factors such as lipoproteins, lipopolysaccharides, and peptidoglycans.[4,25,26] The outer membrane of spirochetes and gram-negative bacteria serves as a permeability barrier.[27] In the case of *Leptospira,* after leaving general circulation, it is in contact with the cells of the proximal tubular region (**Figure 4**).

Pathophysiological observations suggest that these components of the outer membrane may play a fundamental role in the pathogenesis of leptospirosis.[27] Some endotoxins located in this membrane may be responsible for affecting host immunity, which could cause renal failure in patients. Due to its location on the cell surface, the OMP's (Outer Membrane Proteins) of *Leptospira*, are probably important in virulence and host-pathogen interactions, impairing tubular function and producing inflammation.[5] Several OMP´s (LipL32, LipL21, LipL45, LipL31, OmpL1, Flagellin/FlaB1, LipL36, LipL41, LipL71, LipL25 LigA, among others) of pathogenic Leptospires have been described and located in the proximal tubules and the interstitium of animals[5,26] (**Figure 4**). OMP´s activate the Tumor Necrosis Factor-alpha TNF-α, in addition to interleukin IL-1β, which is a potent immunological proinflammatory cytokine.[26,28–31]

Leptospira OMPs produce renal tubular damage and inflammation through the toll-like innate immunity receptor-dependent pathway (TLR).[32] Leukocyte cells activate Nuclear transcription Factor-kappa B (NFKβ) and Mitogen-Activated Kinase Proteins (MAPK), synthesizing transcription factors for the synthesis and differential induction of chemokines and cytokines essential for tubular inflammation.[31–33] They can also activate the fibrosis pathway associated with the transforming growth factor-beta/Smad that accumulates on the extracellular matrix.[34] Renal leptospirosis disease is, therefore, a model to understand how pathogen-induced tubulointerstitial nephritis and fibrosis occur.[5,35]

The LipL32 external membrane lipoprotein has been identified as being a potent virulence factor and being highly conserved in all pathogenic leptospires. This virulence factor induces interstitial tubule necrosis and nephritis. Immunohistochemical tests have confirmed intense reactivity of LipL32 in proximal tubules of the hamster kidneys, demonstrating that it is a potent immunogen protagonist during renal infection in leptospirosis[35] (**Figure 4**).

Lipl32 directly affects the proximal tubules, increasing the expression of proinflammatory genes and proteins, the production of nitric oxide, and the activation of T cells and TNF-α. Initial studies show that, in human macrophages, these potent

antigens bind to toll-like receptors (TLR2) in the renal tubule tissue, inducing immune reaction and, ultimately interstitial nephritis and tubular necrosis in the kidney.[35]

Few virulence factors involved in renal colonization have been experimentally demonstrated, so their possible role in virulence is unknown; additionally, a decrease in the colonization of pathogenic *Leptospira* has been visualized with strut mutations in some genes such as HtpG, HbpA, and LruA.[15,18] The virulence factors LPS, which are involved in lipid synthesis, and HtpG, which is a probable chaperone with unknown functions, are necessary to cause the disease in the acute model of kidney injury of leptospirosis and are also essential in the colonization of mouse kidneys. The HbpA virulence factor has as its function the acquisition of iron,[1] and the LruA virulence factor is a lipoprotein whose characteristic is that of an apolipoprotein APO AI type, necessary for the inverse transport of cholesterol from the blood to the liver, but there is no defined possible role in the virulence of pathogenic *Leptospira*.[15,30]

Renal pathophysiological mechanisms in leptospirosis

Interstitial tubular nephritis is the most frequent pathological manifestation.[1] Clinically, in human leptospirosis, an acute non-oliguric renal lesion with hypokalemia is observed, and loss of magnesium and sodium usually occurs in human leptospirosis.[26,28] In its early stages, leptospirosis generates characteristic nonoliguric acute renal failure and hypokalemia due to a decrease in proximal sodium reabsorption, with the resulting increase in sodium and potassium excretion at the distal level. If leptospirosis is not treated at this stage, the patient will develop an oliguric renal failure with acute tubular necrosis, which requires dialysis in most cases.[16,1] Several pathophysiological mechanisms have been elucidated: hemodynamic alterations, rupture of the basement membrane, hypovolemia due to loss of water and electrolytes from vomiting, diarrhea, or loss of sensation due to fever, direct injury to the glomerulus, vasculitis, and sometimes rhabdomyolysis.[42] All of these lead to interstitial nephritis with mononuclear infiltrates and acute epithelial tubular necrosis. All the above are associated with elements that suggest renal cell damage that is mediated by bacterial toxins[16,23,26,28] (**Figure 4**).

In animal models, the condition has been defined in two important ion transporters. The first is the sodium/hydrogen exchanger 3 (NH3) located in the proximal tubule of the nephron. An injury in this ion transporter explains the high sodium excretion and, therefore, the polyuria in the initial phase of the illness.[1,23] The second affected transporter is evidenced by the increased in the expression of the sodium/potassium/2 chlorine transporter (NaK2Cl), which is in the loop of Henle,[23] as a countermeasure. Several authors[4] have indicated oliguria, shock, platelet disease, plasma potassium> 4 mEq/L, plasma creatinine> 3 mg/dl, and abnormal thoracic auscultation as criteria of poor prognosis for patients with leptospirosis. The evolution of renal failure due to leptospirosis is versatile, in this, prognostic factors of each patient and the adequate supply of specific treatment for pathogenic *Leptospira* played an important role. Cases of acute anicteric renal failure can be self-limited and heal within a few days without dialysis. From a general point of view, the nitrogen compounds in the blood and thrombocytes are restored in two weeks, the protein in urine and the clearance of creatinine in three months, and the urinary concentration in six months.[2,4,26,30]

Laboratory data

As mentioned, in cases of leptospirosis, the kidneys are usually the most affected organs.[1] This is evidenced in the clinical laboratory data of patients with severe infections such as increased conjugated bilirubin, which results mostly in jaundice.[12,14] Mild thrombocytopenia is also evident,[17,20,21] as are changes in the urinary sediment (leukocytes, erythrocytes, hyaline or granular cylinders), Haemoglobin and red cell counts,[51,52] proteinuria in non-nephrotic range, rhabdomyolysis, hypervolemia, in some cases pyuria and hematuria due to damage in the glomerular endothelium, increased blood urea nitrogen (BUN), increased creatinine levels, and increased protein in the urine.[24] When water intake is low due to nausea and frequent excretion of urine, combined, they can cause severe dehydration. Patients are at risk of oliguria and renal failure which is a frequent cause of death in areas where peritoneal dialysis or hemodialysis is not available.[14,30]

CONCLUSION

In the last ten years, significant advances have been made in understanding the renal pathophysiology of leptospirosis, although much remains to be known. The collection of articles compiled in this research topic shows progress in our limited understanding of the pathogenesis and virulence factors involved in renal damage due to *Leptospira*. This information will support the development of new therapeutic approaches and clinical performance in renal failure caused by *Leptospira* Finally, current genomic studies shed more and more light on the most important aspects of its pathogenicity, and the analysis of its genome is one of the keys to elucidating this new knowledge and better understanding the biology and virulence of this bacterium.[1]

CONTRIBUTIONS

Rafael Guillermo Villarreal-Julio: Main authorship, conception of the idea, writing, drafting, and submission of the manuscript. Enderson Murillo Ramos, Rene Ramírez-García, Ronald Guillermo Peláez-Sánchez, and Piedad Matilde Agudelo-Flórez contributed to the writing and revision of the paper. All authors contributed to the editorial revision of the paper and approved its final version.

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RESUMEN. A nivel mundial, la leptospirosis es la zoonosis de mayor prevalencia. Aunque la amplia gama de manifestaciones clínicas de la leptospirosis en humanos está bien documentada, el conocimiento de los mecanismos a través de los cuales este patógeno causa enfermedad renal sigue siendo limitado. Esta revisión narrativa de la literatura científica presenta estudios experimentales de fisiopatología y enfermedad renal en la leptospirosis, tanto en humanos como en animales y los resultados muestran que los factores de virulencia están involucrados en la colonización renal, lo que puede contribuir al daño renal al inducir nefritis tubular intersticial que es la más frecuente manifestación patológica. Además de la lesión renal aguda no oligúrica con hipopotasemia y pérdida de magnesio y sodio. Finalmente, se concluye que, en la leptospirosis, la lesión inicial en el riñón es causada por el daño a la membrana celular de las células de la región tubular proximal por factores de virulencia patógena de *Leptospira*, exacerbando así la respuesta inmune.
Palabras clave: Factores de virulencia, Insuficiencia renal, *Leptospira*, Leptospirosis, Patogénesis.