# Leptospirosis: an update - parte 2 of 2: pathogenesis, clinical aspects, diagnosis and treatment

# Leptospirose: uma actualização - parte 2 de 2: patogénese, aspectos clínicos, diagnóstico e tratamento

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**SUMMARY**
Leptospirosis belongs to the category of neglected infectious diseases and, due to its great epidemic potential, its local distribution in tropical regions is of extreme importance. It is a worldwide public health problem, known for the emergence and reappearance of the disease, lack of sanitary conditions and its abandonment. Human infections usually occur after skin contact with soil and/or water that has been contaminated by the urine of chronically infected

mammals. The clinical manifestations of the disease range from mild fever, chills and flu-like symptoms to acute forms of the disease. Based on these brief considerations, this article - part 2 of 2 - aims to discuss the biological, ecoepidemiological, prophylactic and control aspects of leptospirosis in Brazil.

**Keywords**: leptospirosis, public health, clinical protocols.

**RESUMO**
A leptospirose pertence à categoria das doenças infecciosas negligenciadas e, devido ao seu grande potencial epidémico, a sua distribuição local em regiões tropicais é de extrema importância. É um problema de saúde pública mundial, conhecido pelo aparecimento e reaparição da doença, falta de condições sanitárias e o seu abandono. As infecções humanas ocorrem geralmente após o contacto da pele com o solo e/ou água contaminada pela urina de mamíferos cronicamente infectados. As manifestações clínicas da doença variam desde a febre ligeira, arrepios e sintomas semelhantes aos da gripe até às formas agudas da doença. Com base nestas breves considerações, este artigo - parte 2 de 2 - visa discutir os aspectos biológicos, ecoepidemiológicos, profiláticos e de controlo da leptospirose no Brasil.

**Palavras-chave:** leptospirose, saúde pública, protocolos clínicos.

## 1 INTRODUCTION

Leptospirosis is a feverish infectious disease of abrupt onset that has variable clinical manifestations, from subtle to severe forms that lead to death. It is responsible for about 58,900 deaths and more than one million cases annually reported (COSTA *et al*., 2015), (TORGERSON *et al*., 2015). Leptospirosis is undernotified and under-diagnosed for several reasons, among them being the difficulty of professionals to distinguish its clinical manifestations similar to other potentially endemic tropical diseases - with great possibilities of differential diagnosis in its anicteric form, the most prevalent one - added to the lac of availability and limitations of laboratory services for adequate diagnosis of the numerous serovars of pathogenic species (VIJAYACHARI, SUGUNAN, SHRIRAM, 2008; ISA *et al*., 2014). The objective of this article - part 2 of 2- is to present a review of the establishment of infection, illness and diagnostic approach for their appropriate therapeutic treatment.

## 2 PATHOGENESIS

The great human susceptibility to leptospirosis is due to the fact that the same individual can contract it several times during his life. However, the infection is caused by different serovars, since the acquired immunity is directed against a specific type and does not protect

the organism against others. The severity of the condition depends on variables such as: parasite inoculum, infectivity, pathogenicity of the species and immune response of the host.

It is well known that the pathogenic capacity of microorganisms is extremely related to the invasive capacity of the bacteria and to the toxins that are released in the infection and organ injury. Although the molecular bases of pathogenic *Leptospira* spp are still poorly clarified, it is known that there is a wide variety of proteins involved in cell and tissue invasion and adhesion that may represent potential virulence factors (SUN, LIU, YAN, 2020). Although it is a gram-negative bacterium, no pilis of adhesion were found in its external cell wall, but other characteristics of the bacterium may constitute potential adhesion factors such as, for example, the outer membrane proteins (OMPs).

So far, the only gene that represents a virulence factor consistent with Koch's molecular postulate is loa22, which encodes a OMP of a function not yet known (EVANGELISTA, COBURN, 2010). In addition to the adherence factors, the noted invasive enzymes such as collagenase and metalopeptidase explain the powerful invasive capacity of the bacteria.

Numerous metaloptidase encoding genes were observed in *L. interrogans* with the ability to hydrolyze fibronectins, laminins and collagen. Although they do not have a specific gene coding for exotoxins, *leptospiras* have LPS, which is considered an endotoxin in the cell wall of gram-negative bacteria with significant toxicity to mammals and one of the main causes of pathogenic changes by *E. coli*, *Shigella* and *Salmonella spp* (SUN, LIU, YAN, 2020). The ability to induce apoptosis in macrophages via Fas/FasL has already been shown as its antifagocytosis mechanism. Five types of *L. interrogans* hemolysins have been associated with it, in addition to intense production of IL-1, IL-6 and TNF-alpha (classically fundamental in the pathophysiology of fever), as well as with apoptosis and lesions of the cytothelium endothelium membrane of blood vessels, pulmonary epithelium and liver (SUN, LIU, YAN, 2020).

The onset of infection occurs with the penetration of *Leptospira spp*. into the human body through wounds or abrasions of the skin and intact mucous membranes, mainly conjunctival and oral mucosa. Then, it proliferates and crosses other tissues until it reaches the blood, when the so-called leptospiremia phase begins. While it spreads hematogenically and invades practically all tissues and organs, the inflammatory response triggered by the infection produces a large amount of cytokines and interleukins, which will result in high fever with intense chills.

If the individual is not immune, the microorganism escapes the immune response mediated by complement, through the connection to the H-factor, a potent inhibitor of this system. Thus, it resists phagocytosis and death by macrophages, neutrophils and monocytes.

However, also due to the recognition of the pathogen by defense cells of the organism and through chemical mediators, the humoral response is activated and stimulates the production of IgM class antibodies. Seroconversion can occur 5-7 days after the onset of the disease, sometimes only after 10 days. The most effective way to protect against *Leptospira spp*. infection is the production of serovar-specific LPS antibodies that neutralize *leptospires*.

At the beginning of the immune phase there is a recrudescence of fever and the disappearance of *Leptospira* in biological fluids (except urine). However, the bacteria persists in several organs, mainly in kidneys, where it can remain latent for months, and even years, on occasion. In addition to acquired immunity, innate immunity may be involved in neutralizing antigens through Toll type receptors, like TLR2 and TLR4 (EVANGELISTA, COBURN, 2010). In this second, immune, phase, several reactive manifestations can occur, such as aseptic meningitis characterized by headache, vomiting, mental confusion and uveitis. Manifestations affecting other systems may also be present depending on the individual's immune response and the damage caused by the bacteria in the leptospiremia phase. The duration of the second phase varies from 4 to 30 days.

The primary lesion in leptospirosis appears to be damage to the cell membrane mediated by unknown factors, possibly by *leptospiral* proteins and/or toxic cellular components. Lesions in the cellular membrane can result in serious consequences to the host, such as loss of integrity, ischemia and necrosis, leading to important organ dysfunctions (DEBRITO, SILVA, ABREU, 2018). The wide range of more serious manifestations arise mainly from damage to the endothelial lining of small blood vessels, but the mechanisms are still little known.

Experimental studies show that pathogenic agentes or their proteins are capable of activating endothelial cells and breaking down their structure and barrier function, which would allow the dissemination of the microorganism. The high plasma levels of soluble E selectin and von Willebrand factor in patients with leptospirosis suggest the activation of endothelial cells. Then, coagulopathies of consumption may occur with the presence of high levels of markers of coagulation activity (thrombin-antithrombin complex, fragment 1 and 2 of prothrombin, D-dimer) and decrease of anticoagulation markers (antithrombin, protein C), potentiated with the presence of fibrinolytic activity disorder. Disseminated intravascular coagulation has also been reported. In several organs, hemorrhagic manifestations of varying intensity are observed (mainly in the skin, kidneys, lungs and liver), being associated to thrombocytopenia in several studies. Although it seems likely that thrombocytopenia is secondary to excess consumption, the exact physiopathogenic mechanism of this laboratory change has not yet been fully made clear. Analyzing tissues of human lungs affected by pulmonary hemorrhage, immunoglobulin

deposits, platelet aggregation and activated endothelium complement were observed, while histology reveals edema.

Liver lesions may be better seen in histopathological analysis, which may show focal necrosis, foci of inflammation, bile stoppers. However, no widespread hepatic necrosis is observed. Despite the possibility of several concomitant complications of the disease, the kidneys are the most affected organs, with acute renal failure (ARF) being detected in 16 to 40% of patients, with turbulo-interstitial nephritis being the most common clinical and pathological manifestation (DEBRITO, SILVA, ABREU, 2018).

However, the laboratory findings of ARF present in this disease are unique, due to disorders of the expression of various carriers along the nephron (such as proximal sodium-hydrogen-3 exchanger, aquaporins 1 and 2, Na+K+ ATPase and Na-K-2Cl), inhibiting the reabsorption of sodium in the proximal tubules, increasing the distal sodium input, with consequent potassium depletion. Therefore, it is an ARF associated with hypopotassemia and polyuria. The loss of magnesium in urine is also associated with leptospirosis nephropathy. In this sense, with increased serum creatinine and urea levels and continuous intravascular volume loss, patients may develop acute tubular necrosis and interstitial nephritis.

In view of this, the junction of the triad of severe leptospirosis involvement (renal insufficiency, jaundice and hemorrhagic alterations) will compose the classic Weil's Syndrome. In these cases, the pathological process of renal injury begins with an interstitial nephritis caused by the bacteria and/or its toxins, aggravated by hypoperfusion caused by the bacteria: (1) generalized capillary endothelial lesion that causes loss of fluid to the interstitial space, (2) decrease in water intake, (3) bleeding, (4) vomiting, (5) diarrhea and other losses.

Existing rhabdomyolysis can potentiate kidney injury, with increased nitrogen products and consequent azotemia. The hemorrhagic disorders are also processes resulting from capillary endothelial injury, aggravated by thrombocytopenia and liver alterations. Jaundice is mainly caused by the lesion of hepatocytes, impairing the process of bilirubin excretion, with intrahepatic cholestasis and predominance of the increase in the direct fraction. The leptospirosis jaundice is also, to a lesser degree, a result of bilirubin transport deficiency, hemolysis (infrequent), acute renal injury and reabsorption of hemorrhages.

## 3 NATURAL HISTORY AND CLINICAL FINDINGS

The clinical evolution of leptospirosis varies significantly, from asymptomatic forms and subclinical conditions to severe conditions that can lead to death. After the entry of the pathogen into the human body, the incubation period is estimated to be, on average, from 5 to

14 days, but may vary from 1 to 30 days. The challenges of clinical diagnosis of leptospirosis are due to the presentation of clinical signs and symptoms that simulate many other diseases with endemic potential.

The disease manifestations can be grouped in two categories: early or anicteric phase and late or icteric phase.

3.1 EARLY OR ANICTERIC PHASE

It corresponds to 85-90% of cases and presents as an acute febrile syndrome, but is poorly diagnosed and reported at this stage, and is often diagnosed as "viral", "flu syndrome" or seasonal endemic diseases such as dengue fever. Reflex of the leptospiremia period occurs the abrupt onset of fever and other symptoms that are commonly associated, such as frontal and retroorbital headache (75-100% of cases), asthenia, anorexia, náusea and vomiting. This phase is usually self-limited and regresses within 7 days. Occulalgia, hyperemia and conjunctival hemorrhage, photophobia, arthralgia, bone pain, sore throat and cough may also occur. In addition, exanthema with components of papular, macular, purpuri or urticariform erythema may appear in the tibial region or in the trunk (10 to 20%). The hepatomegaly, lymphadenopathy and splenomegaly evolution is present in up to 20% of cases.

Therefore, it is important to investigate signs and symptoms that may help differentiate leptospirosis in the anicteric phase from other acute febrile diseases. At the end of this phase, a conjunctival suffusion appears in 30% of the patients, which evolves to conjunctival edema along the palpebral fissures and hyperemia. In addition, leptospirosis is associated with strong pain in the calves and lumbar region. However, none of these clinical manifestations cited is significantly specific and sensitive to be pathognomonic.

The end of the acute stage is characterized by rapid defervescence, and there may be a cure, or a progression to the immune phase which will take place with a later increase in fever intensity. Although less frequent, in an anicteric form, severe clinical manifestations may appear, such as neurological and ophthalmological conditions. Aseptic meningitis is the most common neurological involvement, while uveitis is the most common ocular involvement, but with good prognosis, with recovery of vision initially compromised. The evolution to renal failure is extremely rare, differently from that observed in the icteric form (SPERBER, SCHLEUPNER, 1989).

3.2 LATE OR ICTERIC PHASE

This leptospirosis phase occurs in up to 15% of patients and the disease evolves into more severe clinical forms after the first week or earlier in fulminant forms. It also presents

symptoms described in the anicteric phase, such as intense myalgias mainly in calves, remitting fever and headache. Hepatomegaly in this phase is present in up to 70% of the cases, whereas splenomegaly is found in 20% of cases.

Weil's syndrome is the name given to the triad of classical clinical manifestations of severe leptospirosis: jaundice, hemorrhagic disorders and renal failure, with lethality in 5 to 40% of patients (VIJAYACHARI, SUGUNAN, SHRIRAM, 2008). Between the 3rd and 7th day of the disease it is common to see a characteristic orange coloring (rubinic jaundice) due to endothelial lesion of the capillaries, which can evolve to an ictero-hemorrhagic form, and is therefore a sign of worsening of the condition. Hemorrhagic phenomena can occur that vary in intensity, from the appearance of petechiae to hemoptysis. However, it is essential that professionals do not expect a change in skin color to investigate hemorrhagic complications and acute renal failure, since they can also occur in anicteric patients. In addition, it is also possible that there is the appearance of rubinical jaundice alone in the late phase. A very characteristic finding in this phase is hypocalemic acute renal failure and not oliguric.

The bleeding, besides coming from the endothelial capillary lesions aggravated by thrombocytopenia, is probably a reflection of other alterations not yet fully elucidated, such as von Willebrand's factor. In this perspective, an extremely worrying picture is the Pulmonary Hemorrhage Syndrome, which may be present in 20 to 70% of patients (KARPAGAM, GENESHI, 2020), characterized by acute alveolar-capillary injury and massive pulmonary bleeding, being increasingly considered as a distinct and fearful complication of the late phase of leptospirosis, with a lethality higher than 50% (GOUVEIA *et al*, 2008; MCBRIDE *et al*., 2005; CDC, 2020). In addition, the disease can cause Acute Respiratory Distress Syndrome (ARDS) in the presence or absence of bleeding. Therefore, in patients who present fever, chest pain, respiratory discomfort with dry cough or hemoptoic expectoration, lung involvement by leptospirosis should be suspected, since these conditions often precede jaundice and renal failure and there is the possibility of death already in the first 24 hours of hospitalization (BRAZIL, 2014).

## 4 COMPLICATIONS AND ATYPICAL FORMS

Leptospirosis can evolve with frequent complications in its severe form: other types of hemorrhagic diathesis, anemia, dehydration, acute tubular necrosis, pancreatitis, myocarditis, heart failure, metabolic and hydroelectrolytic disorders that can cause shock and arrhythmias; and neurological problems such as delirium, hallucinations and signs of meningeal irritation. In cases of aseptic meningitis, *Leptospira spp*. is often reported as an etiology to be investigated

(SPERBER, SCHLEUPNER, 1989). Although less frequently, facial paralysis, Guillain-Barré syndrome, myelitis, encephalitis, nystagmus, seizures, spasticity and central visual disturbances, rhabdomyolysis, autoimmune hemolytic anemia, thrombocytopenic purpura, hemolytic uremic syndrome may also occur (RAJAPAKSE *et al*., 2015).

Leptospirosis in pregnant women can course with signs of severity, leading to significant fetal and maternal morbidity and mortality: abortion, congenital leptospirosis, postpartum haemorrhage and sepsis (RAJAPAKSE *et al*., 2015). The clinical presentation of the disease may mimic other viral, bacterial and parasitic infections, acute hepatic steatosis, pregnancy-induced hypertension and HELLP syndrome. Due to the unusual presentation, leptospirosis in pregnancy is often misdiagnosed and usually underreported (PULIYATH, SINGH, 2012; RAHIMI *et al*, 2018).

## 5 DIFFERENTIAL DIAGNOSIS

Since leptospirosis is a disease with a broad clinical spectrum and its clinical manifestations are not very specific, there are several differential diagnoses to be considered, depending on the form of clinical presentation (VINETZ, 2001). In the early phase, one should think mainly about: dengue and other arbovirosis, influenza, flu syndrome, coxsackiosis, viral and bacterial meningoencephalitis, malaria, acute Chagas disease, toxoplasmosis, typhoid fever, urinary infection, polymyositis and tropical pyomyositis. In late stage leptospirosis, it is important to differentiate: acute viral hepatitis, severe dengue fever, yellow fever, hantavirus (pulmonary and renal hemorrhagic forms), *Plasmodium falciparum* malaria, infectious endocarditis, rhyquetsiosis, acute pyelonephritis, acute appendicitis, acute cholecystitis, choledocholithiasis, typhoid fever, hemolytic-uremic syndrome and sepsis, especially by *Staphylococcus aureus* in children. In the severe pulmonary form of leptospirosis, the the main differential diagnosis is hantavirus respiratory syndrome. The differentiation is based on the sum of clinical and epidemiological data and the results of complementary tests.

## 6 DIAGNOSTICS

For the diagnosis of leptospirosis it is important to perform laboratory tests for the following reasons: (1) to confirm the diagnosis, since, due to the non-specific clinical manifestations, professionals usually have difficulty distinguishing it from other diseases; (2) epidemiological and public health reasons, because by understanding which are the most common serovars, sources of transmission, reservoirs and location, strategies to confront the disease are more easily elaborated.

Available laboratory methods for the specific diagnosis of leptospira are: serologic tests, culture of contaminated tissues and fluids, dark field microscopy, polymerase chain reaction (PCR) and immunohistochemistry (tissues fixed in formalin, preferably kidney) (CDC, 2020). However, current methods have limited feasibility, so laboratory confirmation is not required for the initiation of treatment. In the case of the icterohemorrhagic form, a well-gathered history and a careful physical examination can contribute to an accurate diagnosis of the disease.

## 7 SPECIFIC LABORATORY TESTS

### 7.1 DIRECT DETECTION METHODS

These examinations consist of the visualization or direct detection of the organism itself or of its antigens in body fluids.

The method of choice will depend on the stage of the illness the individual is in. In the early phase, visualization can be done in the blood by means of dark field microscopy (common microscopies do not allow visualization of leptospira), having a sensitivity of 40% and specificity of 61.5%. However, it has the disadvantage of being useful only when performed by professionals with considerable technical experience. The detection of the microorganism DNA, through PCR, allows a diagnosis of the acute phase even before the appearance of IgM in the host.

However, it is expensive and only available in reference and/or research centers. Besides these, another possible way is isolation in culture from blood, cerebrospinal fluid or peritoneal dialysis fluid in the first 10 days of disease (leptospiremia phase). The difficulties of this method are due to the need of special means, such as Fletcher and Stuart, taking some weeks to have a definitive result (positive or negative), so there is only a retrospective diagnosis. From the late stage, around the second week of illness, although *Leptospira* sp can be isolated from the urine for a period of up to 3 months, the various technical difficulties in performing culture tests make its use uncommon. Besides the urinary elimination of leptospira being intermittent and in small amounts, it is necessary that the urine is alkaline and directed to the culture medium within 2 hours after urination, otherwise the pathogen will die at acidic pH. If the uroculture is viable and necessary for the professionals, the material can be obtained in a correct way with the administration to the patient of a teaspoon of bicarbonate every 4 hours for 2 days, and with the release of the final result between 2 weeks and one month.

### 7.2 INDIRECT DETECTION METHODS

Indirect methods are based on immunological mechanisms, with identification of the antibody reaction with antigens or leptospira itself, and the determination of titers will depend on the relative concentrations and strength of the reaction. Since direct detection of leptospira tends to be slow and of average reliability, serology is usually the most appropriate form of diagnosis. For a correct interpretation it is necessary to keep in mind that a negative result does not exclude leptospirosis and a positive serology does not represent a current infection, since detectable titers of antibodies appear about 5-10 days after the onset of the disease and may remain detectable for long periods. This reasoning becomes even more fundamental in endemic areas. In view of this, for the investigation of the acute disease, it is suggested that samples of clotted blood (or serum) be taken at 2 times, with an interval of 2 weeks between them (taking into account a probable date of onset of the disease and the time to serum conversion). After serological pairing, the diagnosis is confirmed with the presence of elevation of at least 4 times the previous value or when there is serum conversion (no detectable titre in the first sample and the second positive sample).

However, a single titre of at least 1:200 (above the cut-off point) after the onset of symptoms already suggests acute infection. In addition, a titre of 1:800 in the presence of a compatible clinic suggests strong evidence of recent or ongoing infection. The Microagglutination Test (MAT) is the gold standard for diagnosis because of its unsurpassed specificity over other diagnostic methods. Its specificity is higher than 97% and has sensitivity around 75%, but unfortunately there is a need to keep leptospires alive in the laboratory, which is only possible in specialized laboratories.

The ELISA immunoenzymatic assay is the most widely used and several assays are available (there are commercial kits with antigens already fixed), presents high sensitivity (93%) and specificity (94%), being able to detect the IgM antibody just after the fifth day of the disease onset. The disadvantage of the ELISA is that, besides not giving the indication of the infective serovar as in the MAT, since it is based on a gender specific antigen, some of its test systems are less specific and can present cross reactions with other diseases. Whenever possible, serology associated with PCR is indicated. Macroagglutination testing is an easy and inexpensive test, available in several laboratories. It shows good sensitivity in the immune phase, but low specificity. It is performed by macroscopic plate agglutination reaction after addition of patient serum to a formalin inactivated *L. interrogans* suspension. It is useful to identify negative cases. In short, serological test results are important, but should always be analyzed in conjunction with epidemiological (possible exposure, risk factors and others) and clinical presentation data.

7.3 NON-SPECIFIC EXAMS

Other tests are necessary to evaluate the course of disease manifestations in various organs and systems and also help differentiate from other diseases. Thus, complete blood count and biochemical tests can be requested, such as total bilirubin and fractions, gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (FA), urea, creatinine, Na+, K+, creatinokinase (CPK) and their fractions. If necessary, chest radiography, electrocardiogram (ECG), cerebrospinal fluid examination and arterial gasometry should also be requested. Laboratory alterations are usually unspecific in the early phase, but in the late phase more typical patterns of the disease appear.

It is common for hemograms to present, besides neutrophilia with left deviation, a leukocytosis that can reach leukemoid reaction levels. Leukocytosis with neutrophilia helps in the differential diagnosis with dengue, which is followed by leukopenia and lymphomonocytosis. If plaquetopenia and anemia appear, it is indicative of severe leptospirosis. Often there is normochromic anemia. Hematocrit evaluation helps estimate the degree of dehydration and the need for blood transfusion, especially if hemorrhagic manifestations with hemodynamic alterations occur. It is common to increase the hemosedimentation rate, helping in the differential diagnosis of acute icteric hepatitis and yellow fever, whose values are usually very low. Another useful exam for the differential diagnosis are the hepatic aminotransferases that show an elevation of up to 3 or 5 times the reference values (usually not more than 500 IU/Dl), as opposed to the values 10 times above normal found in acute viral hepatitis and yellow fever. The activated partial thromboplastin (PTTa) and prothrombin (TAP) times are also usually increased.

The icteric form of leptospirosis is associated with an increase in direct bilirubin, aiding in differential diagnosis with dengue fever. However, increased bilirubin may be present in viral hepatitis, and laboratory tests that differentiate leptospirosis from those are: increased CPK, moderate elevation of AST and ALT, leukocytosis with left shift. Arterial gasometry reveals metabolic acidosis with drop of bicarbonate and hypoxemia. The type 1 urine examination reveals microscopic hematuria, proteinuria, low urinary density and leukocytosis. Hypokalemia is a fundamental finding that differentiates it from other diseases that have acute renal failure.

It is important to keep in mind the evaluation of nitrogen slags (urea and creatinine), hydroelectrolytic alterations and acidobasic balance are also essential for the proper therapeutic conduct, due to the risk of acute renal failure requiring dialysis. In addition, chest radiography may show congestion and alveolar or lobar infiltrate unilaterally or bilaterally, and may prevent the course of serious complications, since pathologically these findings may represent alveolar

hemorrhage, ARDS or pulmonary edema. Another warning for signs of early manifestation of pulmonary bleeding is the observation of decreased hematocrit and hemoglobin values during serial examinations without exteriorization of bleeding. In cardiac complications of severe disease may be present in the ECG: fibrillation, atrioventricular block and changes in ventricular repolarization. Elevation of the myocardial fraction of the CPK is usually observed when there is myocarditis.

## 8 TREATMENT

Most cases of leptospirosis do not require treatment with antimicrobials, as they are self-limiting. Pain or fever medications containing acetylsalicylic acid that may increase the risk of bleeding and should not be used. Non-hormonal anti-inflammatory drugs should also not be used because of the risk of side effects such as digestive bleeding and allergic reactions (MARTINS, CASTIÑEIRAS, 2020). However, a large number of cases develop into the severe form of the disease and systemic complications, characterizing a high morbidity and mortality. Severe cases need immediate hospitalization and, in addition to the use of antibiotics, intensive care therapy with renal replacement therapy, blood transfusion and ventilatory support may be required. In general terms, the treatment is based on: (1) Antibiotic therapy, (2) Correction of dehydration and hydroelectrolytic and acidobasic balance disorders, (3) Treatment of renal dysfunction, and (4) Intensive care.

### 8.1 ANTIBIOTIC THERAPY

The clinical efficacy of antimicrobials in the treatment of leptospirosis in both mild and severe forms has not been fully established and still remains a controversial subject (EDWARDS *et al*, 1988; WATT *et al.*, 1988; COSTA *et al.*, 2003; EDWARDS, LEVETT, 2004; PAPPAS, CASCIO, 2006; KARPAGAM, GANESH, 2020; SUPUTTAMONGKOL et *al.*, 2004; PANAPHUT *et al.*, 2003). The antibiotic therapy is indicated in any period of the disease, but the period of greater effectiveness is in the first 5 days of the onset of symptoms. In the care of patients with acute febrile syndrome suspected of leptospirosis in an anicteric form, the therapeutic scheme indicated according to the Surveillance Guide of the Ministry of Health (2019) are doxycycline 100 mg, orally, every 12 hours for 5 to 7 days or amoxicillin 500 mg, orally, every 8 hours for 5 to 7 days. In children, amoxicillin 50 mg/kg/day should be administered orally at intervals of 6 to 8 hours for 5 to 7 days; doxycycline should not be used in children under 8 years of age. Doxycycline should also not be used in pregnant women, amoxicillin being the drug of choice in the above-mentioned doses.

However, a diferente, scheme is also described by Uptodate (NICK, 2014b). So, the authors suggest tht patients who have warning signs for the severe form of the disease (icteric form) should be hospitalized and treated with age-specific intravenous antibiotic therapy, which should last at least 7 days. Therefore, for adults, it is indicated. Therefore, for adults, it is indicated: penicillin (1.5 million IU, intravenous (IV), every 6 hours), doxycycline (100mg, IV, twice a day), ceftriaxone (1 to 2 g, IV, once a day), or cefotaxime (1g, IV, every 6 hours). For hospitalized children with severe illness, it is recommended to use: penicillin (250.000 to 400.000 IU/Kg, IV, per day, equally divided into 4 to 6 doses - maximum of 6 to 12 million IU/day), doxycycline (4mg/kg, IV, per day, in two doses equally divided - maximum of 200mg/day), ceftriaxone (80 to 100mg/kg, IV, once a day - maximum of 2g daily), or Cefotaxime (100 to 150 mg/kg, IV, equally divided into 3 or 4 doses per day). For children with intolerance to previous drugs, an alternative is azithromycin (10mg/kg, IV, on the first day-maximum 500mg/day and 5mg/kg/day, IV, on the 5 subsequent days (maximum 250mg/day). In severe form of leptospirosis, the therapeutic schemes are: penicillin G crystalline 1,500,000UI, intravenously, every 6 hours for at least 7 days or ampicillin 1g, intravenously, every 6 hours for at least 7 days or ceftriaxone 1g, intravenously, every 24 hours for at least 7 days or cefotaxime 1g, intravenously, every 6 hours for at least 7 days (Isa *et al,* 2014). In severe form in pregnant women, the treatment with Penicillin or ceftriaxone, or cefotaxime. As in other diseases caused by spirochetes, treatment of patients with leptospirosis with penicillin can trigger a Jarisch-Herxheimer reaction; however, such an adverse event is rarely (Butler, 2017; CDC, 2020; Guerrier, D'Ortenzio, 2013). Besides azithromycin, clarithromycin can be an alternative if there is counterindication to the above recommendations.

## 8.2 CORRECTION OF DEHYDRATION AND HYDROELECTROLYTIC AND ACIDOBASIC BALANCE DISORDERS

The treatment for severe cases of dehydration is volume replacement therapy with 0.9% saline solution or lactate ringer, to prevent progress to hypovolemic shock. The solution should be administered in bolus, through two peripheral venous accesses. If hypotension and oliguria (or anuria) persist, central venous pressure (CVP) monitoring is indicated to guide volume replacement and more intensive support measures. Kidney injury with hypokalemia is frequent in leptospirosis, so monitoring of serum potassium value is necessary to avoid all complications that may arise from its imbalance. In case of severe deficit (< 3 mEq/L), the potassium must be restored. In cases of arterial gasometry changes with PaO2 lower than 60 mmHg or respiratory

rate higher than 28 incursions/minute and $SatO_2$ lower than 92%, early ventilatory support should be offered.

## 8.3 TREATMENT OF RENAL DYSFUNCTION

After hydration, about 500 ml of SF 0.9% in bolus repeated 3 times, the diuresis should be measured. Most patients recover with satisfactory urinary output (> 0.5 ml/Kg/h), characterizing acute non oliguric renal failure. Thus, treatment should be continued with: maintenance of hydration with 80mL/kg/day of 0.9% saline solution and monitoring of blood pressure and respiratory pattern, in case it is necessary, respectively, to start vasoactive drug or restart the evaluation of the case and treatments.

If there is no response, with maintenance of urinary output <0.5 mL/Kg/h, diuretic stimulation with a single dose of 100mg furosemide can be done intravenously. A considerable number of patients present diuresis after these measures. It is also necessary to be attentive to the indication criteria for dialysis (hemodialysis, peritoneal dialysis or hemoperfusion), after all, its early and daily insertion in these cases prevents sequelae and reduces mortality.

## 8.4 INTENSIVE CARE

In severe cases, hospitalization is essential to provide intensive care to severe patients who evolve with more serious complications, such as pulmonary hemorrhage, ARDS, myocarditis, septic shock and others. Leptospirosis can cause severe but transient ARDS, having a better prognosis than other causes of ARDS. Some patients were successfully treated with extracorporeal membrane oxygenation (VANDROUX *et al*., 2019).

A study conducted in Brazil demonstrated that independent risk factors in leptospirosis for ICU admission include tachypnea, hypotension and ARF. Ceftriaxone was a protective factor for ICU admission, suggesting that its use may prevent severe forms (DAHER *et al*., 2016). The use of corticosteroids in severe forms of leptospirosis, despite being recommended by some authors, still remains controversial (SMITH et. al, 2019). In fact, to avoid the worst prognosis, the good management of Weil's syndrome depends on intensive support measures, such as volume replacement, potassium replacement when necessary, follow-up of renal and pulmonary function, already discussed previously (SMITH et. al, 2019).

## REFERENCES

ANDRADE, Lúcia; CLETO, Sérgio; SEGURO, Antonio C. Door-to-dialysis time and daily hemodialysis in patients with leptospirosis: impact on mortality. Clinical Journal of the American Society of Nephrology, v. 2, n. 4, p. 739-744, 2007.

BRASIL. Ministry of Health. Secretariat of Health Surveillance. Department of Surveillance of Transmissible Diseases. Leptospirosis: diagnosis and clinical management/Ministry of Health, Secretariat of Health Surveillance. Department of Surveillance of Transmissible Diseases. - Brasília: Ministry of Health, 2014. 44 p.

BUTLER, T. The Jarisch-Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis. Am J Trop Med Hyg. 2017 Jan 11;96(1):46-52.

CENTERS FOR DISEASE CONTROL AND PREVENTION. Leptospirosis. Available at: https://www.cdc.gov/leptospirosis/pdf/fs-leptospirosis-clinicians-eng-508.pdf. Acessed in: September 16, 2020 a.

COSTA E, LOPES AA, SACRAMENTO E, COSTA YA, ELIANA DIAS MATOS, LOPES MB, BINA JC. Penicillin at the late stage of leptospirosis: a randomized controlled trial. Rev Inst Med Trop Sao Paulo. May-Jun 2003;45(3):141-5.

DAHER EF, ABREU KLS, SILVA JUNIOR GB. Acute renal failure associated with leptospirosis. Brazilian Journal of Nephrology 2010, 32(4); 408-15

DE BRITO T, SILVA AMG, ABREU PAE. Pathology and pathogenesis of human leptospirosis: a commented review. Rev Inst Med Trop Sao Paulo. 60:e23, 2018.

DE FRANCESCO DAHER, E., SOARES, D.S., DE MENEZES FERNANDES, A.T.B. *et al.*Risk factors for intensive care unit admission in patients with severe leptospirosis: a comparative study according to patients' severity. BMC Infectious Diseases 16:40, 2016.

EDWARDS CN, LEVETT PN. Prevention and treatment of leptospirosis. Expert Rev Anti Infect Ther. Apr;2(2):293-8, 2004.

EDWARDS CN, NICHOLSON GD, HASSELL TA, EVERARD CO, CALLENDER J,EVANGELISTA KV, COBURN J. Leptospira as an emerging pathogen: a review of its biology, pathogenesis and host immune responses. Future Microbiol. 2010 Sep;5(9):1413-25.

EDWARDS CN, NICHOLSON GD, HASSELL TA, EVERARD CO, CALLENDER J. Penicillin therapy in icteric leptospirosis. Am J Trop Med Hyg. 1988 Oct;39(4):388-90.

GOUVEIA EL, METCALFE J, DE CARVALHO AL, AIRES TS, VILLASBOAS-BISNETO JC, QUEIRROZ A *et al*. Leptospirosis-associated severe pulmonary hemorrhagic syndrome, Salvador, Brazil. Emerg Emerg Infect Dis J. 2008; 14:505-8.

GUERRIER G, D'ORTENZIO E. The Jarisch-Herxheimer Reaction in Leptospirosis: A Systematic Review. PLoS One. 2013; 8(3): e59266. doi: 10.1371/journal.pone.0059266.

HAAKE DA, LEVETT PN. Leptospirosis in humans. Curr Top Microbiol Immunol. 2015; 387:65-97.

HARTSKEERL RA, WAGENAAR JP. Leptospirosis. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill, 2015. Disponible in: http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79737529. Accessed August 23, 2015.

ISA, SAMSON EJIJI *et al*. A 21-year-old student with fever and profound jaundice. PLoS Negl Trop Dis, v. 8, n. 1, p. e2534, 2014.

KARPAGAM KB, GANESH B. Leptospirosis: a neglected tropical zoonotic infection of public health importance-an updated review. European Journal of Clinical Microbiology & Infectious Diseases 39:835-46, 2020.

LEVETT PN E HAAKE DA. Leptospira Species (Leptospirosis). In Mandell GL, Bennett JE, Doln R *et al* (editors). Mandell, Douglas, and Benett's Principles and Practive of Infectious Diseases, 7th ed. Elsevier, 2010.

MCBRIDE AJA, ATHANAZIO DA, REIS MG, KO AI. Leptospirosis. Curr Infect Dis. 2005 Oct;18(5):376-86.

NICK D. Epidemiology, microbiology, clinical manifestations, and diagnosis of leptospirosis. Uptodate. 2014a.

NICK D. Treatment and prevention of leptospirosis. Uptodate. 2014b. Disponível em: www.uptodate.com. Acesso em 9/07/2015.

PANAPHUT T, DOMRONGKITCHAIPORN S, VIBHAGOOL A,THINKAMROP B, SUSAENGRAT W. Ceftriaxone compared with sodium penicillin g for treatment of severe leptospirosis. Clin Infect Dis. 2003 Jun 15;36(12):1507-13.

PAPPAS G, CASCIO A. Optimal treatment of leptospirosis: queries and projections. International Journal of Antimicrobial Agents 28: 491-6, 2006.

PICARDEAU M. Diagnosis and epidemiology of leptospirosis. Médecine et maladies infectiauses 2013.

Puliyath G, Singh S. Leptospirosis in pregnancy. European Journal of Clinical Microbiology & Infectious Diseases 31: 2491-6, 2012.

RAHIMI R, OMAR E, TUAN SOH TS, MOHD NAWI SFA, NOOR S. Leptospirosis in pregnancy: a lesson in subtlety. Malays J Pathol 40(2):169-173, 2018.

RAJAPAKSE S, RODRIGO C, BALAJI K, FERNANDO SD. Atypical manifestations of leptospirosis

RIOS GONÇALVES AJ, CARVALHO JEM, GUEDES E SILVA JB, ROZEMBAUM R, VIEIRA ARM. Hemoptysis and acute respiratory distress syndrome as cause of death in leptospirosis. Changes in clinical and anatomopathological patterns. Arq Bras Med 1993; 67:161-166.

SHIEH WJ, EDWARS C, LEVETT PN, ZAKI SR. Leptospirosis. In Guerrant Rl, Walker DH, Weller PF (editors). Tropical Infectious Diseases: Principals, Pathogens e Practice, 3rd ed. Elsevier, 2011.

SILVA JJP. Leptospirosis. In Tavares W and Marinho LAC (editors). Routines of Diagnosis and Treatment of Infectious and Parasitic Diseases, 3rd ed, São Paulo. Atheneu, 2012.

SIQUEIRA-BATISTA R, GOMES AP, ENGEL DC, BARROSO DE, SANTOS SS. Leptospirosis. In: Siqueira-Batista R, Gomes AP, Igreja RP, Huggins DW. Tropical Medicine. Current Approach to Infectious and Parasitic Diseases. Rio de Janeiro, Editora Cultura Médica, 2001.

SMITH S, LIU YU-HSUAN, CARTER A, KENNEDY BJ, DERMEDGOGLOU A, *et al*. Severe leptospirosis in tropical Australia: Optimising intensive care unit management to reduce mortality. PLoS Negl Trop Dis . 2019 Dec 2;13(12):e0007929. doi: 10.1371/journal.pntd.0007929.

SPERBER SJ, SCHLEUPNER CJ. Leptospirosis: a forgotten cause of aseptic meningitis and multisystem febrile illness. South Med J. 1989 Oct;82(10):1285-8.

SUN, AI-HUA; LIU, XIAO-XIANG; YAN, JIE. Leptospirosis is an invasive infectious and systemic inflammatory disease. Biomedical Journal, 2020.

SUPUTTAMONGKOL Y, NIWATTAYAKUL K, SUTTINONT C, LOSUWANALUK K, LIMPAIBOON R, *et. al*. An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis. Clin Infect Dis. 2004 Nov 15;39(10):1417-24.

VANDROUX D, CHANAREILLE P, DELMAS B, GAÜZÈRE BERNARD-ALEX, ALLOU N, *et al*. Acute respiratory distress syndrome in leptospirosis. Journal of Critical Care 5:165-9, 2019.

VIJAYACHARI, P.; SUGUNAN, A. P.; SHRIRAM, A. N. Leptospirosis: an emerging global public health problem. Journal of biosciences, v. 33, n. 4, p. 557-569, 2008.

VINETZ JM. Leptospirosis. Curr Infect Dis. 2001 Oct;14(5):527-38.

WATT G, PADRE LP, TUAZON ML, CALUBAQUIB C, SANTIAGO E, RANOA CP, LAUGHLIN LW. Placebo-controlled trial of intravenous penicillin for severe and late leptospirosis. Lancet. 1988 Feb 27;1(8583):433-5.