Leptospirosis: A Neglected Tropical Disease with Global Implications

Sasirekha Arangannan, Sudhakar Pachiappan, GokulaKannan Shanmugam, Rabeya Akbarbasha, Nidharshna Senthil

Department of Pharmacology, Swamy Vivekanandha College of Pharmacy, Elayampalayam-637 205, Namakkal, Tamil Nadu, India

Corresponding Author
Sasirekha Arangannan
P.G. Research Scholar
Department of Pharmacology
Swamy Vivekanandha College of Pharmacy,
Elayampalaym-637 205, Tamil Nadu, India

Abstract: Leptospirosis is a zoonotic bacterial infection caused by *Leptospira interrogans*, transmitted through direct or indirect contact with contaminated water, soil, or animal reservoirs. The disease presents a broad clinical diapason, ranging from mild febrile illness to severe complications such as Weil's syndrome, characterized by jaundice, acute kidney injury (AKI), and hemorrhagic manifestations. The pathogen employs various immune evasion strategies, including complement inhibition and endothelial damage, leading to vascular leakage and multi-organ failure. Opinion relies on a combination of serological and molecular ways, with rapid tests similar to the Leptodipstick assay furnishing early detection advantages. Effective treatment includes antibiotics like doxycycline and penicillin, alongside probative care for organ dysfunction. Preventive strategies concentrate on environmental control, vaccination of livestock, and public health interventions to reduce human exposure. Given its increasing global prevalence, particularly in tropical regions, better diagnostic methods and targeted therapies are essential for better disease management and control.

Keywords: *Environmental Contamination, Immune Evasion, Leptospirosis, Leptospira interrogans, Rapid diagnostics*.

1. Introduction

Leptospirosis is a bacterial infection caused by Leptospira species, substantially *Leptospira interrogans* (pathogenic) and *Leptospira biflexa* (nonpathogenic)[1]. The L. interrogans complex includes 23 serogroups and around 210 serovars. The disease is a zoonotic infection, where humans are incidental hosts in a cycle involving wild and domestic animals[2]. Rodents serve as the primary reservoir, excreting bacteria in their urine, polluting water and soil, and facilitating transmission to humans and other animals[3]. Factors such as increased human-animal contact, habitat encroachment, and climate change elevate the threat of leptospirosis[4]. The global wildlife trade and ecotourism also contribute to disease spread, exposing humans to defiled surroundings. Also, climate-induced disasters like floods and hurricanes enhance bacterial survival and dispersion, increasing infection rates[5]. Clinically, leptospirosis manifests in two phases. The initial phase lasts 3–7 days and includes fever, headache, muscle pain (especially in calves), nausea, vomiting, malaise, and conjunctival greenishness[6]. Around 80–90% of patients recover after this phase, but 10% progress to the severe alternate phase, known as Weil's syndrome[7]. This stage can last from 4 to 30 days and presents with life-threatening complications, including jaundice, acute kidney injury (AKI), meningitis, and pulmonary haemorrhage[8]. Hemorrhagic manifestations, in particular, have become a major concern, with an increasing number of cases reported worldwide. Leptospirosis remains a significant global health issue, especially in tropical and subtropical regions. Proper sanitation, rodent control, defensive measures, and early diagnosis are crucial for preventing and managing the disease[9].

2. Symptoms

In both children and adults, leptospirosis commonly presents with fever, myalgia, and headache. Lethargy, emesis, abdominal pain, photophobia, arthralgia, cough, diarrhea, or constipation also may occur (Figure 1)[10].

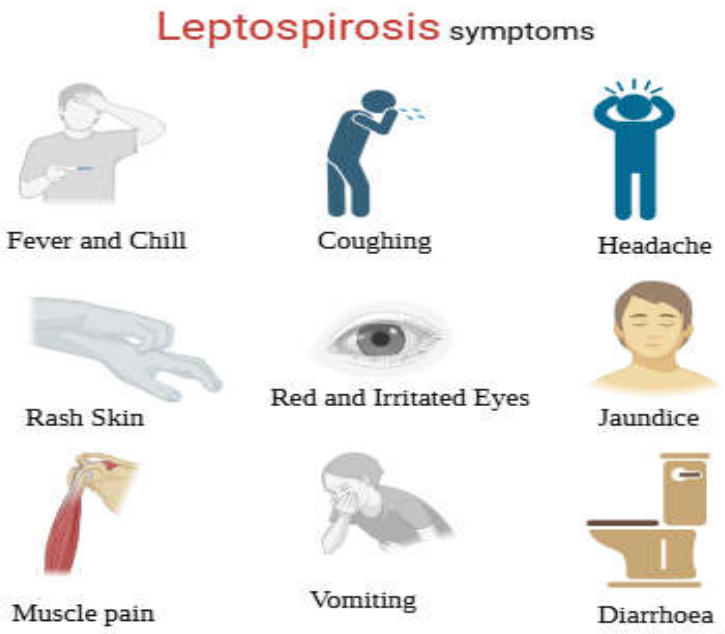

Figure 1: Symptoms of leptospirosis

2. Historical Background

Leptospirois was first described over a century ago in 1886 by Adolph Weil in Heidelberg, Germany[11]. It proved four cases of men suffering from jaundice, acute kidney injury (AKI), and hemorrhagic instantiations, which led to the disease being named Weil's disease or Weil's syndrome. However, historical substantiation suggests that leptospirosis was long before its formal identification[12]. In ancient China, records indicate the presence of a disease affecting rice planters with clinical symptoms suggesting leptosirosis[13]. Also, in the 17th century, an outbreak of hemorrhagic fever passed among native Americans in New England, USA[14]. Leptospirosis is widely common in equatorial regions, with a significant proportion (73%) of cases found in southeastern asia, the eastern part of sub-saharan Africa, Caribbean islands, and the pacific region[15]. It is common among the rural farming populations and impoverished urban and semi-urban populations, particularly affecting young male adults.

3. Entry of Leptospirosis

Leptospirosis enters the body through broken skin, through mucous membranes, or by breathing in contaminated air. The bacterium enters the bloodstream to various organs[16]. The rodents, especially rats, and other mammals, such as cattle, pigs, scapegoats, hamsters, dogs, jackals, foxes, marsupials, and raccoons, also serve as hosts to the bacteria. The disease is transmitted from animals to humans through infected urine or through a terrain that's contaminated with the microorganism[17]. The animal reservoirs carry the microorganisms for a long time in their proximal tubules and exfoliate them in their urine (Figure 2).

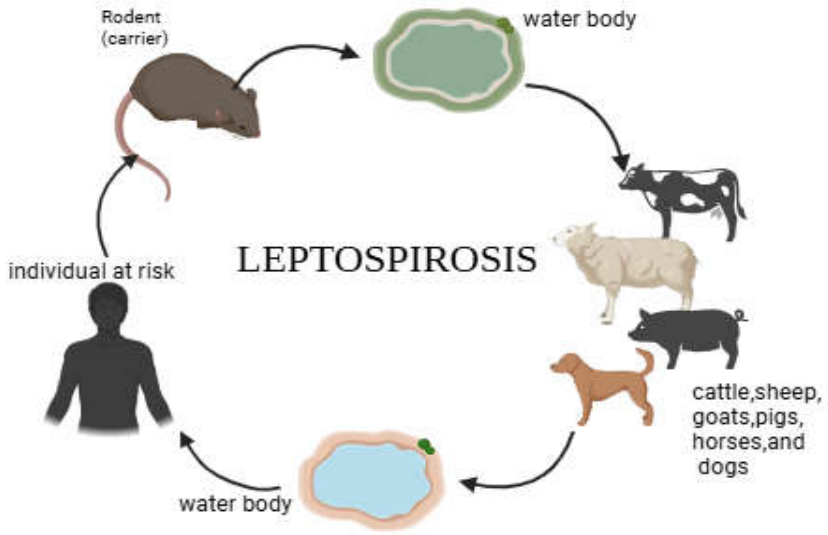

Figure 2: Transmission cycle of leptospirosis

4. Immune evasion of Leptospirosis

Pathogenic *Leptospira* have developed multiple immune evasion strategies to establish infection and persist in the host. They resist phagocytosis by neutrophils by inhibiting myeloperoxidase (MPO) activity through the LipL21 protein, preventing oxidative killing[18]. To shirk complement-intermediated destruction, *Leptospira* prisoners host complement controllers similar to Factor H (FH) and C4b-binding protein (C4BP) via surface proteins like LenA, LenB, LigA, and LcpA, thereby inhibiting complement activation. Also, they acquire plasminogen and convert it into plasmin, which degrades crucial immune components like C3b and C4b, reducing opsonisation and immune recognition[19]. The secretion of metalloproteases and thermolysin further neutralises complement proteins (C3, C6–C9), preventing membrane attack complex (MAC) formation and immune-mediated lysis[20]. By binding host immunoglobulins and disrupting immune signaling, *Leptospira* effectively shirk antibody responses, allowing them to spread and cause severe systemic disease (Figure 3). These evasion mechanisms punctuate the complexity of leptospiral pathogenesis and the challenges in developing effective treatments and vaccines[20].

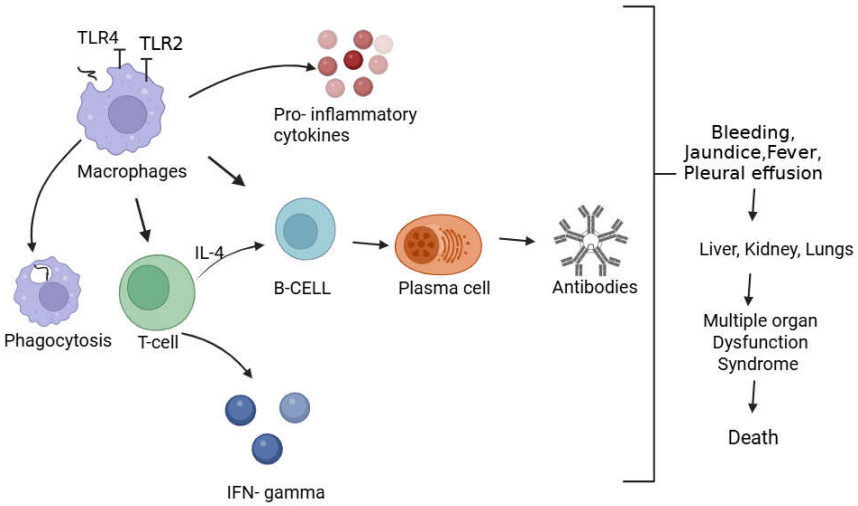

Figure 3: Immune activation leading to multi-organ dysfunction in Leptospiral infection

5. Endothelial damage and vascular damage

Leptospirosis causes significant endothelial and vascular damage, contributing to complications such as haemorrhage, vascular leakage, and multi-organ failure[21]. *Leptospira* directly foray endothelial cells, dismembering intercellular junctions and weakening vascular integrity. Bacterial external membrane proteins (OMPs) and poisons induce endothelial apoptosis and dysfunction, adding permeability. This leads to widespread vascular leakage, hypotension, and organ damage [22]. Also, the infection triggers an intense inflammatory response, with elevated cytokines similar to TNF-α, IL-1, and IL-6, further promoting endothelial activation and vascular permeability. Coagulation abnormalities, including disseminated intravascular coagulation (DIC), occur due to endothelial injury, leading to platelet dysfunction, bloodied clot conformation, and increased threat of haemorrhage [23]. In severe cases, pulmonary haemorrhage syndrome (SPHS) develops due to endothelial rupture and alveolar capillary damage, resulting in respiratory distress and high mortality. The combined effects of direct bacterial irruption, inflammatory responses, and coagulation disturbances make endothelial damage a critical factor in the pathogenesis of severe leptospirosis[24].

6. Organ specific damage

It can affect multiple organs due to its capability to circulate through the bloodstream and invade tissues [25] (Figure.03). The pathogenesis varies depending on the severity of the disease, which ranges from mild flu-like symptoms to severe complications [26](Weil's disease or severe pulmonary hemorrhagic syndrome).

6.1. Liver pathology in leptospirosis

leptospirosis invasion-bacteria attaching to hepatocytes: *Leptospira* bacteria enter the bloodstream through mucosal membranes or skin scrapes after exposure to contaminated water or animal reservoirs (especially rodents). Formerly in circulation, the bacteria target the liver and infiltrate the space of Disse (a small area between hepatocytes and sinusoidal endothelial cells). *Leptospira* attach to hepatocytes using adhesins and surface proteins, similar to LigA, LigB, and LenA, which help them adhere and evade the immune system[27]. The bacteria can penetrate between liver cells, damaging intercellular junctions, increasing vascular permeability, and allowing bacterial dissemination[28].

Inflammatory response—immune cell infiltration, hepatocyte degeneration, and vascular congestion: The host immune system recognises the bacterial invasion, leading to a strong inflammatory response. Neutrophils, macrophages, and lymphocytes infiltrate liver tissue to fight the infection[29]. These immune cells release pro-inflammatory cytokines similar to TNF-α, IL-1, and IL-6, which further increase inflammation and damage liver cells. Leptospira toxins and outer membrane proteins induce hepatocyte apoptosis and necrosis, leading to liver dysfunction[30]. Vascular congestion occurs due to endothelial damage and capillary leakage, further worsening hepatocyte injury.

Jaundice development-bile leakage and intrahepatic cholestasis: As hepatocytes are damaged and destroyed, their capability to process and excrete bilirubin is impaired. Disruption of bile canaliculi causes bile leakage into surrounding liver tissues. Intrahepatic cholestasis occurs, where bile flow is obstructed inside the liver, leading to bilirubin accumulation in the bloodstream (hyperbilirubinemia)[31]. As bilirubin levels rise, it deposits in the skin, eyes, and mucous membranes, causing jaundice, a hallmark symptom of severe leptospirosis.

6.2. Pulmonary pathology of leptospirosis

Pulmonary involvement in leptospirosis is primarily driven by poison-intermediated capillary vasculitis and immune responses. The presence of *leptospiral* toxins in circulation contributes to endothelial dysfunction, leading to haemorrhage and vascular leakage[32]. Although the bacterial cargo in the lungs is fairly low, damage is probably due to circulating toxins from distant organs similar to the liver. Also, inhibition of the Na^+/K^+ pump disrupts alveolar fluid concurrence, resulting in pulmonary oedema and respiratory distress. Alterations in ion transport, including dropped epithelial sodium channel (ENaC) expression and increased Na-K-2Cl (NKCC) co-transporter activity, further impair lung function[33]. Cytokines such as TNF-α and IL-1 play a role in modifying ion channels, aggravating pulmonary damage. Increased expression of adhesion molecules like VCAM-1 and ICAM-1, along with immune receptor activation, promotes leukocyte reclamation and inflammation[34]. Thrombocytopenia may further contribute to hemorrhagic instantiations. Severe cases frequently present with pulmonary haemorrhage, a major cause of death in leptospirosis. Endothelial inflammation, immune

complex deposit, and platelet activation are crucial mechanisms underlying this condition[35]. Mortality rates remain high, with mechanical ventilation identified as a significant threat factor for death.

7. Diagnosis

The diagnosis of leptospirosis is based on the clinical features and epidemiological data, further confirmed by laboratory tests.

Direct observation : The direct observation method involves isolating *leptospira* from blood, cerebrospinal fluid, or peritoneal dialysate fluid within the first 10 days of infection[8]. Urine cultures may also be used during the first week, as the bacterial load can vary from 10^2 to 10^6 *leptospires* per milliliter. However, dark field microscopy, through cost-effective means, is infrequently available, limiting its practical use.

Nucleic acid-based rapid tests : Nucleic acid-based rapid tests, such as polymerase chain reaction (PCR), have been developed and tested in clinical studies[36]. While largely sensitive, PCR remains uncommon in routine practice due to high costs and the need for strict quality controls. PCR detection limits range from 100 to 1,000,000 bacteria per milliliter of blood or urine, arresting the presence of *leptospira* but unfit to determine its serovar[37].

Isothermal methods: The loop-mediated isothermal amplification technique has shown promise due to its effectiveness[38]. However, its cost remains analogous to real-time PCR and it isn't clear when these tests are going to be really economically competitive.

Rapid test using antibiotics: Rapid antibody-based tests utilize *leptospira* surface recombinant proteins and lipoproteins as antigens[39]. While enzyme-linked immunosorbent assay (ELISA) methods offer good perceptivity, the different circulating *leptospira* strains can affect antigen recognition. Despite variations in performance, studies suggest that ELISA-based methods can detect anti-*leptospira* antibodies earlier than the microscopic agglutination test (MAT), offering an advantage in early diagnosis[40].

Leptodipstick assay : The Leptodipstic assay is a rapid immunochromatographic test designed for early detection of *leptospira* antigens in biological samples[41]. It's grounded on a principle of antigen-antibody interaction, where specific antibodies immobilised on a dipstick capture *leptospira* antigens present in the sample, producing a visible colour change if the test is positive.

8. Treatment and management

The early opinion and prompt performance of respectable remedies are vital in managing *leptospirosis*. Supportive care plays a vital role, and specific measures should be initiated as soon as possible[40]. Mild cases are treated with doxycycline or penicillin, with paracetamol for symptom relief. Severe *leptospirosis*, including dau's complaint, requires hospitalization with aggressive fluid failure. Cases with renal failure may suffer peritoneal dialysis, hemodialysis, or

a nonstop renal remedy. Several antimicrobial agents, including penicillins, tetracyclines, streptomycin, azithromycin, and cephalosporins, have shown in vitro effectiveness against *leptospira*. Studies suggest ceftriaxone may reduce severe complaint progression, but meta-analyses haven't verified a significant impact on mortality[42].

Cardiac monitoring is essential for cases with myocarditis, as arrhythmias may do. Pulmonary hemorrhage, a major cause of death, may bear oxygen remedy, mechanical ventilation, nitric oxide inhalation, or desmopressin[43]. Jaundice generally resolves within five weeks; in rare cases of liver failure, tube exchange may be salutary. Diagnosing pancreatitis in severe leptospirosis is challenging due to elevated serum amylase situations, taking evidence via imaging before standard treatment. Cases with verified meningitis should admit intravenous penicillin. Early and effective antibiotic therapy, along with comprehensive supportive care, is essential for reducing complications and improving survival[44]. Cardiac monitoring is essential for cases with myocarditis, as arrhythmias may occur. Pulmonary hemorrhage, a major cause of death, may bear oxygen remedy, mechanical ventilation, nitric oxide inhalation, or desmopressin. Jaundice generally resolves within five weeks; in rare cases of liver failure, tube exchange may be salutary[45]. Diagnosing pancreatitis in severe leptospirosis is challenging due to elevated serum amylase situations, taking sustantiation via imaging before standard treatment. Cases with verified meningitis should admit intravenous penicillin. Beforehand and effective antibiotic therapy, along with comprehensive supportive care, is essential for reducing complications and perfecting survival.

9. Prevention and control

Prevention of leptospirosis depends upon a convention of the original epidemiology and relating infection sources[45]. Effective measures include controlling force beast populations, moderating the environment, and using defensive apparel. Immunisation of livestock with killed bacterins is common but provides short-term protection and doesn't help infection or transmission. Public health juggernauts should target high-threat groups like agrarian workers, veterinarians, and adventure excursioists.

10. Conclusion

Leptospirosis is a serious zoonotic disease with a wide clinical spectrum, ranging from mild illness to life-threatening complications like Weil’s syndrome and multi-organ failure. Early diagnosis through rapid tests like the Leptodipstick assay, along with timely antibiotic treatment, significantly improves outcomes. Preventive measures, including sanitation, rodent control, and protective strategies for high-risk groups, are crucial in reducing transmission. While vaccines exist for animals, more effective human vaccines are needed. With climate change and urbanization increasing its spread, a comprehensive approach involving early detection, improved treatments, and strong public health initiatives is essential for effective disease control.

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