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Leptospirosis: An Overview

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INTRODUCTION

Infectious diseases transmitted via vectors or animals (Zoonotic disease) remain a leading cause of high morbidity and mortality. According to a meta-analysis, 60.3% of new infectious diseases are caused by the rapid spread of zoonotic pathogens from animals to humans and involve the interactions of humans, animals, and the environment. Various types of animals are reservoirs of zoonotic pathogens such as *Leptospira* that can circulate in different ecosystems (Urbanskas et al. 2022). Leptospirosis (LPS) is a neglected zoonotic disease recognised as the biggest public health threat around the globe with high prevalence. LPS caused by gram-negative, aerobic and slow-growing bacteria of genus *Leptospira* spp. in a group of spirochetes. The genus *Leptospira* contains numerous numbers of species which are pathogenic, intermediate and some are non-pathogenic strains based on genotypic classification as shown in Fig. 1 (Desvars et al. 2011). Serovars and serogroups are classified on a serological basis and around 300 serovars are grouped into the several numbers of serogroups (Picardeau 2017). *Leptospira* is usually 0.1 µm wide and 6-20 µm long with pointed ends bent into hook-like shapes which differentiate from other spirochetes (Samrot et al. 2021). It can grow at an optimum temperature of 28-30ºC and pH of 6.8-7.6 which affects all mammalian species mostly living in a tropical climate where environmental conditions favor the prolonged survival of pathogen and transmission in poor resources and developing countries. It affects all the mammalian species and infected animals may also act as the reservoir hosts which may transmit the infection directly or indirectly depending upon the infection source (Bandara et al. 2014; Pappas et al. 2008).

The disease spread through direct contact with contagious secretions (blood, urine, aborted fetus, contaminated water, soil, feed and uterine discharge) of infected animals and distributed throughout the systematic circulation and in various organs (Hajikolaei et al. 2022; Schuller et al. 2015). These organisms enter through mucus membranes of abraded skin, vagina, nose and eyes as shown in Fig. 2 (Sykes et al. 2022).

Leptospira organisms multiply in the liver, kidney, spleen, ocular tissue, central nervous system and genital tract (Ananda et al. 2008). This infection infects humans as well as animals that impact production mainly after heavy rains (Galarde-López et al. 2021; Sud 2021; Haake and Levett 2015). The kidney and liver are the main targets during both acute and chronic phases. In these organs, they can multiply and survive for months (Haake and Levett 2015).

Population groups who are at high risk of getting infection include veterinarians, breeders, dairy farmers, meat workers and laboratory employees. However, indirect exposure to the environment (overcrowding, sanitary conditions) is the most frequent way of human exposure to get *Leptospira* infection (Fernandes et al. 2019). The global epidemiological status of LPS is fragmentary but in humans an estimated 1.03 million infection cases were reported in 2020 (Calvopiña et al. 2022). It's considered as a major cause of economic loss that can be attributed to the cost of treatment, high culling and low pregnancy in animals (Tomckowiack et al. 2022). The diagnoses are only a key step for a better outcome that depends on the sample availability. Various laboratory tests are used for the detection of the LPS include culturing, molecular, serological and microscopic evaluation (Musso and Scola 2013). LPS can better be treated with antibiotics (penicillin, ampicillin, streptomycin, erythromycin, tetracycline and doxycycline) but prevention can reduce the infection risk by taking sanitary measures (Lucheis and Ferreira 2011).

Clinical Manifestation

LPS may exist in 4 forms including per-acute, acute, sub-acute and chronic form. The clinical manifestations of LPS have non-specific symptoms in humans like fever, headache, myalgia, acute heart failure, hemoptysis and several organ injuries (Costa et al. 2015). Other non-specific symptoms are similar to those seen in dengue, hemorrhagic fever, rickettsial infection, malaria and bacterial sepsis. Approximately 10% cases lead to severe disease (Haake and Levett 2015; Adler and Alejandro 2010). In humans, disease is known by various local names like Fort Bragg fever, Rice field fever, Host Pea Picker's fever, Weill's disease, pretibial fever, Sugar cane cutter fever and Swine herder's fever (Rajapakse 2022; Bhatia and Umapathy 2015).

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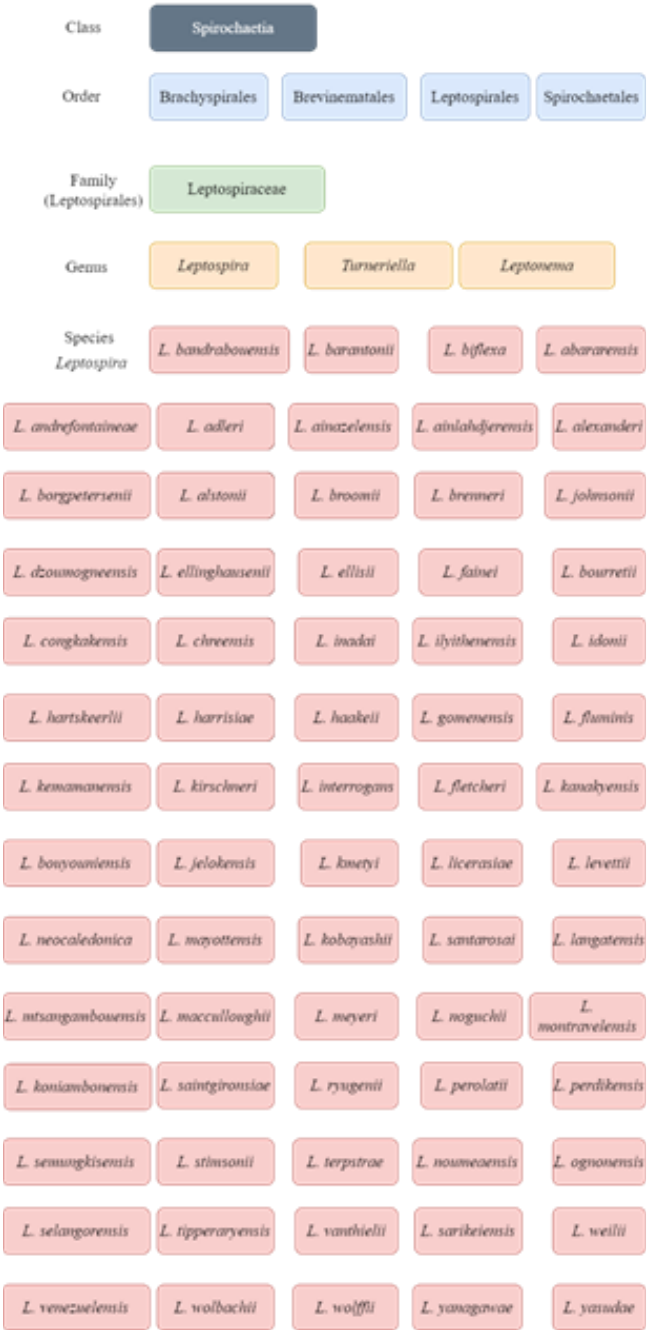

Fig. 1: Taxonomy and Classification of *Leptospira*.

LPS is characterized by a broad range of clinical signs and symptoms in animals with minor differences in affected species. In bovines, it is associated with reproductive problems like stillbirth, abortion, fetus and fetal membrane retention, infertility, low milk yield and calves' death (Correia et al. 2017). Abortion and stillbirth are the most serious clinical events due to pathogenic *Leptospira* infection. Abortion usually occurs during last trimester of pregnancy. Infertility and low milk production occur in pregnant and lactating animals due to the proliferation of *Leptospira* pathogen in the uterus and mammary gland (Rajapakse 2022; Yadeta et al. 2016).

In canines, LPS causes acute infection and has been largely described worldwide. Acute infection associated with serogroups; Icterohaemorrhagiae, Canicole and Grippotyphosa. According to several studies vomiting, lethargy, anorexia, polyuria, weight loss, abdominal pain, diarrhea and dehydration are the most common signs in dogs (Ross 2022; Goldstein 2010). The infection may range from mild febrile illness to life-threatening multisystemic disease which is often characterized by pulmonary hemorrhage and hepatic and renal failure with coagulative disorders (Chacko et al. 2021; Al-Sadi et al. 2015).

Diagnoses

LPS diagnosis is based on history, risk factors and clinical manifestation. Difficult and frequent misdiagnosis of *Leptospira* infection due to similar symptoms of various others diseases makes it the most neglected infectious disease (Chancharoenthana et al. 2022; Tomckowiack et al. 2022). Identification of etiology and confirmation of clinical cases is particularly significant to establish proper preventive measures and appropriate treatment in the herd (Tomckowiack et al. 2022; Martins and Lilenbaum 2017). For the proper diagnosis of LPS laboratory diagnosis is essential (Chancharoenthana et al. 2022).

The diagnosis of LPS is difficult that can be performed by directly identifying spirochetes, their components in body tissues and fluids, and detecting antibodies during clinical phases. Culturing and isolation of pathogens enable for the identification of infectious serovars but it is insensitive and several weeks' incubation is required (Pal, Lema, and Atalel 2022). The majority of LPS patients are diagnosed with serologic tests by using either plasma or serum and serum are most frequently used (Ahmad et al. 2005). Several studies revealed that for the diagnosis of pathogenic *Leptospira* in aborted cattle serum, the sample is collected for antibiotic detection. Laboratory diagnosis includes both direct and indirect identification as shown in Table 1 (Chancharoenthana et al. 2022; Gasem et al. 2020).

LPS diagnosis is difficult because it typically necessitates the pathogen isolation that takes time. LPS diagnostic tests should be accurate, easy to use, cheap, interpret easily, and offer outcomes in a few hours. In addition to a Dark Field Microscopy (DFM), Microscopic agglutination test (MAT) can be a simple procedure with less expensive equipment. LPS-related serovars are identified using MAT. Australis, Autumnalis, Bataviae, Canicola, Ballum, Cynopteri, Grippotyphosa, Sejroe, Hebdomadis, Icterohaemorrhagiae, Panama, Ponoma, Pyrogenes, Tarassovi and nonpathogenic serogroups Semaranga are the few antigens to be used in MAT (Soo et al. 2020; Van De Werve et al. 2013). As the live *Leptospira* are utilized as the material, the method is not standardized. LPS can be biologically diagnosed using ELISA, although the technique has significant drawbacks,

Table 1: Laboratory Diagnostic Tests

Direct Method	Indirect Method
Microscopy	Genus Specific antibody test
Immunohistochemistry	Indirect hemagglutination (IHA)
Immunofluorescence	Enzyme-linked immunosorbent assay (ELISA)
immunoperoxidase	Leptospirosis immunoglobulin (IgM) dipstick
Isolation of Leptospires	Microcapsule agglutination test (MCAT)
Deoxyribonucleic acid (DNA) phase contrast staining	Serovar-specific antibody test
	Microscopic agglutination test (MAT)
Warthin Starry silver stain	
Dark Field Microscopy (DFM)	
Animal Inoculation	
Polymers chain reaction (PCR)	
Loop mediated isothermal amplification (LAMP)	
Next generation sequencing (NGS)	

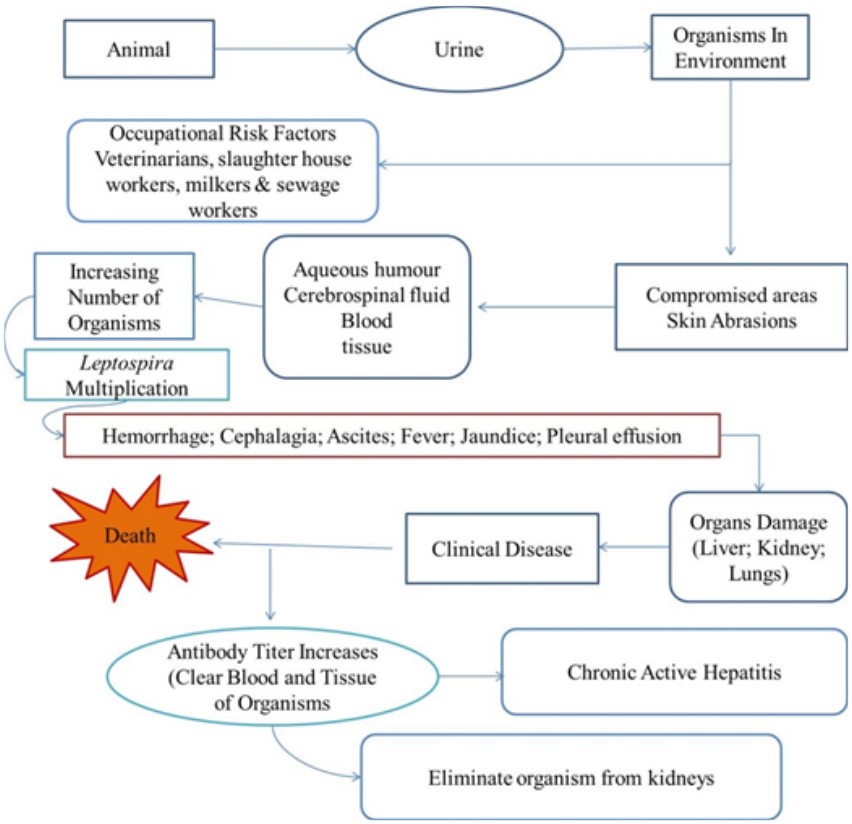

Fig. 2: Transmission and Pathogenesis framework of Leptospirosis (Samrot et al. 2021).

most notably the use of non-pathogen antigen, which makes it possible thatnot all infectious serovars will be detected. By far the most important advantage of PCR is the possibility to confirm the diagnosis of LPS before the appearance of IgM during the early acute phase in infected individuals. Real-time PCR is moreover a quick, sensitive and focused method with lowering the erroneous results from carryover contamination. Cross-reactions caused by the presence of additional diseases could also be found while conducting the ELISA test as shown in Table 2 (Pal et al. 2022; Sykes et al. 2022; Chacko et al. 2021; Budihal and Perwez 2014).

Therapy & Prevention

Treatment of LPS is a big challenge to clear *Leptospira* from tissues. Treatment is usually done with antibiotics and supportive therapies (Ananda et al. 2008). The majority of LPS cases are mild and resolved with antibiotic drugs that are given according to the severity of the illness (Chacko et al. 2021). It's vital to start the treatment to avoid complications until confirmation but the diagnosis must be confirmed (Haake and Levett 2015). In humans, LPS is treated with recommended antibiotics including ampicillin, ceftriaxone and cefotaxime (Panaphut et al. 2003).

Table 2: Laboratory Diagnostic Tests, their targets and Remarks (Sykes et al. 2022; Samrot et al. 2021; Agampodi et al. 2012)

Test	Diagnostic Sample	Target	Remarks
DFM	Urine	*Leptospira*	Low sensitive Require technical expertise
Culture	Blood, Urine	Leptospires	Media Requirement Prolonged incubation Low sensitivity
MAT	Serum	Antibodies against several serovars	Error can occur Live *Leptospira* utilized Suitable for epidemiological purposes High Specificity Can cross validate ELISA finding
ELISA	Serum, Plasma	*Leptospira* IgM, IgG	False Negatives & Positives can occur
DNA (Nucleic acid amplification) test	Blood, Urine, Tissue specimen, CSF	*Leptospira* DNA	Quick Sensitive Low erroneous in result Sensitivity can reduce due to antimicrobial therapy
Histopathology	Kidney tissue specimen	Leptospires	Antimicrobial therapy lead to a false result

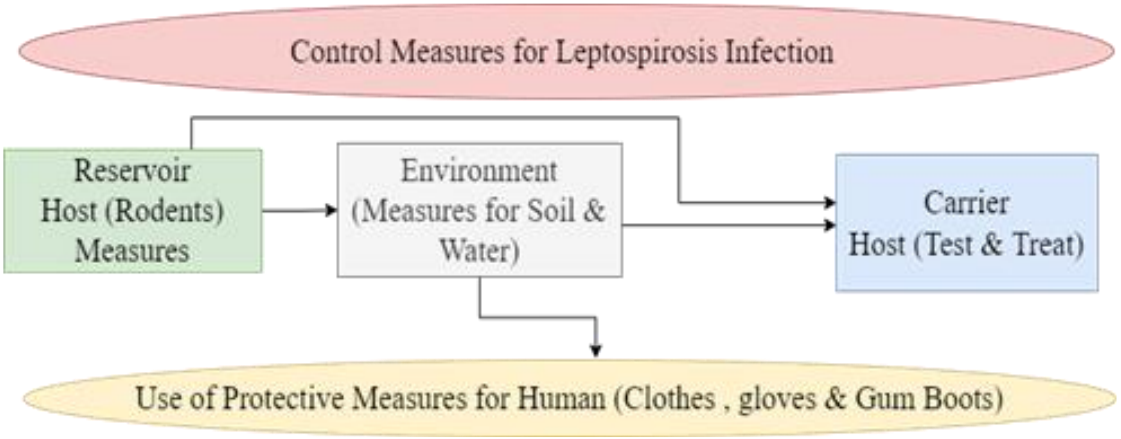

Fig. 3: Control Strategies for Leptospirosis (Vijayachari et al. 2008).

Adult patients with early onset of infection can be treated with azithromycin and doxycycline. Antibiotic therapy is effective within 7-10 days but benzylpenicillin is prescribed only for 5 days. Hypersensitive or allergic patients to the penicillin group can be treated with erythromycin for 5 days and doxycycline for 10 days. It is revealed from previous studies that penicillin G is ineffective to use due to the development of resistance. Tetracycline (doxycycline) in young children, pregnant ladies and kidney dysfunction patients is contraindicated (Lawrence 2022; Brett-Major and Coldren 2012).

In animals, various antibiotics are used including ampicillin, ofloxacin, enrofloxacin, ciprofloxacin, doxycycline, and oxytetracycline for cure in hamsters, swine and cattle (Langston and Heuter 2003). Erythromycin and aminoglycoside are effective but aminoglycosides should be avoided in renal dysfunction (Soo et al. 2020; Langston and Heuter 2003).

Fluid therapy, blood transfusion and other supportive care are also vital that depend on the animal and its needs. Administration of fluids is mostly suggested as the first consideration to correct hypotension, hypovolemia and renal failure. Urine output should be assessed after rehydration. If the hydrated patient's urine output remains low, then it should be treated with diuretics (Bilal et al. 2018; Pappas et al. 2008; Langston and Heuter 2003).

Although many therapies are used to control the transmission of LPS infection and reemergence but preventive measures are always better. The preventive measures include spreading awareness regarding transmission route, avoiding contact with animals, soil, water, and avoid travelling in the endemic areas as much as possible is an ideal path to eradicate LPS. The proper use of protective equipment such as gloves, and boots can prevent the contact of farmers, agriculture workers, animal caretakers, athletic events, and flood relief people with the infectious agents as shown in Fig. 3 (Karpagam and Ganesh 2020; Bavia et al. 2019). These people must be well trained and alert to not get exposed and infected (Jorge et al. 2018). Folks should be advised not to swim in contaminated water bodies and avoid exposure and contact with pets and infected animals. Vaccine design is also a major challenge since 1886 for LPS (Karpagam and Ganesh 2020).

Conclusion

Leptospirosis is a zoonotic but treatable disease found worldwide having major prevalence in developing countries. The disease infects both humans and animals. In humans, it is locally known as Weil's disease. The clinical manifestation and severity of the disease are highly variable. The main source of infection is the urine of contaminated animals. Laboratory tests confirm the diagnosis of infection. Available treatment for the zoonotic diseases involves the use of antibiotics. Sanitary measures are the most important control measures in animals and humans.

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