Review Article **CODEN: AJPCFF** **ISSN: 2321 – 0915**

Asian Journal of Phytomedicine and Clinical Research

Journal home page: www.ajpcrjournal.com

https://doi.org/10.36673/AJPCR.2023.v11.i04.A11

A REVIEW ON LEPTOSPIROSIS

Saumya Srivastava*[1], Nimesh Agrawal[1], Sanch Srivastava[1], Navneet Kumar Verma[1]

[1*]Buddha Institute of Pharmacy, Gida, Gorakhpur, Uttar Pradesh, India.

ABSTRACT

Leptospirosis is a zoonotic illness that can spread quickly, particularly during a period of intense rainfall. It is caused by the bacteria Leptospira. Leptospira interrogans, which has over 200 serovars or serologic variations, is harmful to both people and animals. Leptospirosis is typically contracted by humans from direct contact with the urine of diseased animals or from an environment contaminated with urine. Transmission from person to person happens very infrequently. Leptospirosis can show up as a wide range of clinical symptoms, ranging from a minor ailment that could develop into a dangerous and occasionally fatal condition. Its symptoms can mirror those of a variety of illnesses, including dengue, influenza and other viral hemorrhagic infections. In outbreak situations in particular, it is crucial to make the accurate clinical and laboratory diagnosis as soon as symptoms appear in order to avert severe cases and save lives.

KEYWORDS

Leptospirosis, *Leptospira interrogans* and Serologic Variations.

Author for Correspondence:

Saumya Srivastava,

Buddha Institute of Pharmacy,

Gida, Gorakhpur, Uttar Pradesh, India.

Email: Saumyasrivastava1512@gmail.com

INTRODUCTION

Leptospirosis is an acute bacterial infection that can induce multiple organ involvement and deadly consequences. It is caused by spirochetes from the genus Leptospira[1]. It can be found in temperate, tropical, and subtropical climate zones throughout a large geographic range. The majority of illnesses that arise in the industrialized world are related to recreational exposure to tainted water. It appears that the prevalence is rising in developing nations. This rise in incidence of leptospirosis has been noted in a few countries where it is being monitored[2]. Leptospirosis is endemic to the majority of the countries in South East Asia. Tens of thousands of severe instances of leptospirosis

occur annually worldwide, according to data compiled by the International Leptospirosis Society (ILS) on the disease's occurrence in different nations[3]. Since only a few nations took part in the poll and leptospirosis surveillance is still far from perfect in those nations, this could only be an underestimate. In recent years, there have been several outbreaks of leptospirosis in different countries, especially in South America[4-6] and India[7-11]. A few of these were brought on by natural disasters like floods and cyclones. Leptospirosis is thought to be the most common zoonosis worldwide[12]. Leptospirosis affects numerous other vertebrate species in addition to humans. In humans, it can show up as a broad range of clinical symptoms[13]. Weil's illness is the term used to describe the renally involved icteric leptospirosis syndrome.

Presenting with a significant pulmonary hemorrhage is another recognized clinical type[4,10,11]. Meningitis, abrupt respiratory failure[14], myocarditis[15] and renal failure[16] are a few other consequences. The late consequence of leptospirosis that has lately been identified is uveitis[17,18]. Perhaps the most leptospirosis-related deadly consequence is pulmonary hemorrhage. Patients who have pulmonary hemorrhage in the Andaman Islands have a noticeably higher case fatality ratio than patients who appear with other clinical signs[11]. In China and Korea, serovar Lai, a member of serogroup Icterohaemorrhagiae, has been implicated in leptospirosis cases where hemoptysis is the most common symptom[19]. However, it has also been discovered that other serovars, like Australis, are connected to a comparable clinical presentation[3,20].

The Nicaraguan epidemic in 1995 involved Serovars Canicola and Pomona[21,22]. Following the 1993 superstorm, Orissa, India saw a leptospirosis outbreak accompanied by pulmonary hemorrhage, which was caused by serogroup Canicola[3,8]. A few serovars from the serogroup Grippotyphosa, notably Valbuzzi, have been isolated from leptospirosis cases accompanied by pulmonary hemorrhage in the Andaman Islands[23]. Renal failure is the other most frequent fatal consequence. Leptospiral etiology was shown to be present in a sizable fraction of cases of renal failure seen by the nephrology department in Chennai, India[16]. Conservative approaches, such as symptomatic therapy and preserving fluid and electrolyte balance, can, nevertheless, usually reverse renal failure[11]. Rarely do other issues like meningitis turn deadly.

Myocarditis can occasionally result in deadly cardiac arrhythmias and uncontrollably low blood pressure. In tropical poor nations, leptospirosis is a zoonotic illness that is difficult to eradicate and may even be controlled due to the wide range of animal species that can carry the disease. The bacteria is suited to the tropical climate with lots of rains, where it is frequently hard to keep people safe from animals or contaminated environments. Therefore, the actions that may be performed to lessen the severity of the issue include early case discovery, rapid treatment and raising public health professionals' and the general public's awareness of the disease**.**

HISTORICAL PRESPRECTIVE

Adolf Weil[24] reported a clinical condition in 1886 that included splenomegaly, jaundice, hemorrhages and nephritis. Weil's disease, the term commonly used to describe this sickness, has come to be associated with leptospirosis. For many decades, there have been recognized clinical disorders that bear similarities to Weil's diagnosis of hemorrhagic jaundice. In ancient China, these illnesses were acknowledged as potential workplace risks for rice farmers[25]. Leptospirosis was eventually found to be the cause of several illnesses known by their traditional names in Japan, including akiyami (autumn fever), hasamiyami (autumn fever in Hasami district) and nanukayami (seven day fever). Later research identified leptospiral infection as the cause of several local illnesses in Europe and Australia, including Schlammfieber (mud fever), cane-cutter's disease, and swine-herd's sickness.

As a result, leptospirosis has varied names throughout the world depending on the season,

symptoms, length of illness, or jobs believed to be linked to the condition. Weil's illness was first linked to leptospires in Japan, where coal miners were frequently affected[26]. Inada and Ido were able to effectively infect guinea pigs in 1915, and they were able to grow the pathogen from the blood of the affected animals. Unaware of this development, in October 1915 Huebener and Reiter announced that Weil's disease had been successfully transmitted to guinea pigs. They displayed blood smears stained with Giemsa that had flagella-like bodies. After a span of ten days, Uhlenhuth and Fromme likewise revealed comparable results. Additionally, they noted that the identical spirochaete induced anicteric leptospirosis for the first time.

A few years prior to this, Stimson had reported spiral creatures found in kidney specimens from a patient dyed using the Levadeti technique, which is used to show spirocheats[27]. Stimson's description was acknowledged as the first evidence of leptospira by the World Health Organization Scientific Group on Research in Leptospirosis (1962-1965)[28]. Using a liver samples from a patient who had reportedly died of yellow fever, Naguchi-who was not a doctor-grew a spirochaete. He gave the name Spirochaetaicteroids to this bacterium. It was nearly identical to the causative agent of Weil's disease, and in guinea pig cross-protection experiments, it was impossible to tell the two organisms apart.

After the yellow fever virus was discovered in 1930, it was evident that the two organisms were practically the same and that the patient may have had leptospirosis instead of yellow fever. The organism causing Weil's disease was identified as Spirochaetaicterohaemorrhagiae by the Japanese researchers who first discovered it. Nevertheless, this creature differed significantly from other spirochaetes in terms of appearance and motility. Because of its hooked extremities, Stimson, who was viewing the creature in the kidney specimens, did not think it was a spirochaete and instead gave it the interim name Spirochaetainterrogans. The organism was named Spirochaetaicterogenes by Huebener and Reiter in Germany, and Spirochaeta nodosa by Uhlenhuth and Fromme.

The original term was followed by the French, nevertheless. Weil's disease was first linked to leptospires in Japan, where coal workers were frequently affected by it. The earliest known carriers of leptospires were rodents. Numerous investigations into leptospiral carrier status and seroprevalence in rats have been carried out throughout numerous nations.) The Japanese authors named Spirochaetaicterohaemorrhagiae, arguing that since they were the ones who discovered the organism, only they had the right to name it. In 1917, Naguchi created the genus Leptospira due to the morphological and motility differences. This organism's "long, slender, cylindrical, highly flexible filament with tightly set, regular, shallow spirals" was the distinctive trait he described.

Pillot and Ryter proposed the Leptospiraceae family within the Order of Spirocheatales in 1965. Leptospires were found to be the origin of Weil's disease and soon after, the leptospiral etiology of a number of additional disease types was identified. Among these are "akiyami," or harvest sickness, and "nanukayami," or the Japanese seven-day illness. Rats' function as leprosyspires' carriers was explained by the same Japanese team that identified the disease[26]. Leptospira icterohaemorrhagiae, L. icteroids and L. hebdomadis were the three forms of leptospires that were once thought to exist. These species differed from one another serologically but were similar morphologically[29]. Leptospires were believed to be the cause of Weil's sickness, yellow fever, seven-day fever, and most likely dengue and sand fly fever[29]. Within ten years following the discovery of leptospires, a large portion of the fundamental knowledge that exists today regarding leptospirosis and leptospires was known. During this time, a number of leptospire species were identified, including L. icterohaemorrhagiae, L. canicola, L. grippotyphosa, L. andamana, L. australis, L. bataviae, L. tarassovi, and L. pomona[30,31]. By the 1940s, it was known that leptospirosis in animals could infect humans and

was a significant veterinary issue. Because of military actions in South East Asia, a large amount of data on the ecology of leptospires in tropical countries was generated during the 1950s and 1970s. The earliest known carriers of leptospires were rodents. Numerous investigations into leptospiral carrier status and seroprevalence in rats have been carried out across numerous nations. Russia was the first country to identify the disease in cattle[24]. Numerous facets of the virus's animal transmission were discovered during a series of investigations carried out in Northern Ireland in the 1970s and 1980s by W.A. Ellis and others[32-34]. Many investigations carried out in many nations during that time period produced a wealth of information regarding the dynamics of disease transmission in different domestic animal species. It is now well known that practically all mammalian species, especially aquatic and wild creatures, can harborleptospires and spread infections to humans. Pathogenesis's early research revealed that leptospires are common in the organs. Additionally, the research demonstrated that leptospires bind to platelets; it was believed that this adherence was the reason for the hemorrhages and thrombocytopenia observed in Weil's disease. Soon after the organism was discovered, knowledge about immunity was developed, and it was realized that humoral immunity accounted for the majority of immunity. An immunological agglutination using convalescent sera was described in the first papers. Soon, a number of serological assays were created, such as the latex, haemagglutination and other macroscopic agglutination tests. The standard is still the Microscopic Agglutination Test (MAT), which was created about 70 years ago. In the 1980s, an ELISA test for leptospirosis diagnosis was created[35]. Prior to the development of antibiotics, the only forms of targeted treatment were arsenicals and immunotherapy employing antisera from horses or rabbits. The original attempts to prevent the disease focused on rodent control because rats were the first known animals to carry leptospires. The challenges in control became evident after it was realized that a wide range of animals may harbor the bacterium and serve as the source of infection for humans. By the end of the 19th century, accounts of Weil's illness had begun to surface in Indian literature[36]. Chowdry described a string of jaundice episodes that started in 1892 and lasted for ten years in the Andaman Islands. Although the malaria parasite was not visible in blood smears, Chowdry thought that the cases were malaria. Subsequent investigations revealed that these were, in fact, examples of Weil's illness[29,37]. In 1909, Wolley documented a case series of 40 cases of acute malaria accompanied by jaundice and 17 fatalities among self-supporting Andamanseprisoners[38]. The malaria parasite was not present in the blood smear in this series either. Additionally, Wolley reported seeing moving rod-like entities affixed to red blood cells. Five cases of "toxic jaundice or unknown origin" were documented by de Castro in the Andaman Islands in 1921[39]. He looked for leptospira on blood films, but he was unable to find any. After reviewing these accounts in 1926, Barker came to the conclusion that these instances were, in fact, cases of Weil's sickness. Additionally, he was able to collect microscopic proof that leptospires were present in patient stained blood films. The Andaman islands were the source of the first report of leptospirosis patients with bacteriological confirmation in 1931[37].

In just four months, twenty-four leptospire isolates were taken from 64 Weil's disease patients who were free-living prisoners in Port Blair and the neighboring villages. Leptospirosis cases that were isolated and either confirmed by the organisms' isolation or demonstration, or by serological evidence, were frequently reported from a number of locations, including Calcutta, Assam, and Bombay[40-42]. However, leptospirosis reports after the 1940s remained relatively rare until 1980, and the majority of these reports came from the four metropolises. In the past, the illness was limited to a few locations, including Madras, Bombay, Calcutta, and the Andaman Islands. Reports of human leptospirosis began to surface in the 1980s, both more frequently and in more locations than previously reported. There have been outbreaks in a

number of locations, frequently with significant fatality rates. The amount of accounts that appear in the literature indicates that the disease is getting more and more widespread, despite the lack of a systematic compilation of statistics on incidence. The illness is now known to affect all of the states in the South, West Bengal and Assam in the Eastern Region, Bihar, Uttar Pradesh and Delhi in the North, Maharashtra and Gujarat in the West and the Andaman Islands. Leptospirosis has been identified as a significant public health concern in a number of locations, including Kerala, Tamil Nadu, and the Andaman Islands. Given the nature of the environment and people's lifestyle, leptospirosis poses a constant threat to our population's health, accounting for a significant portion of cases with clinical complications such as renal failure and myocarditis[43-45].

Classification of Leptospira

Leptospiraceae is a family that includes the genera Leptospira, Leptonema and Turneria. The order Spirochaetales is made up of the families Leptospiraceae and Spirochaetaceae (genera Spriochaeta, Cristispira, Borrelia and Treponema). There are currently two distinct classification systems used for Leptospiraceae: one based on phenotypic characters and the other on genetic homology.

Phenotypic classification

The two species (Figure No.1) of the genus Leptospira are the pathogenic L. interrogans and the non-pathogenic L. biflexa. It is common practice to utilize growth at 13ºC and in the presence of 8-azaguanine for speciation[46,47]. While non-pathogenic leptospires grow at 13°C and are resistant to 8-azaguanine, pathogenic leptospires are inhibited in both growth conditions. There are various serovars in both species, and a serovar is the fundamental taxon that is defined by the antigenic composition of its surface[48-50].

When a sufficient quantity of heterologous antigen is absorbed during cross-absorption, at least one of the two antisera consistently retains more than 10% of the homologous titre, indicating that the two strains are distinct serovars. Serogroups are groups of closely similar serovars. Serogroup designation, however, is only meant to be used in laboratories and has no valid taxonomic status. Under the species L.interrogans, more than 250 serovars organized into 25 serogroups have been reported. There are 65 serovars in the species L. biflexa, organized into 38 serogroups.

Strict adherence to the binominal classification scheme is maintained. Leptospira biflexa serovar Patoc in serogroup Semaranga (L. biflexa serovar Patoc in serogroup Semaranga) or Leptospira interrogans serovar icterohaemorrhagiae in serogroup Icterohaemorrhagiae (L. interrogans, serovar Icterohaemorrhagiae in serogroup Icterohaemorrhagiae) are examples of serovar and serogroup names that may be added. To determine a serogroup, a panel of rabbit antisera (group sera) is utilized. The recommended test for determining serovar is the Cross Agglutination Absorption Test (CAAT). A set of monoclonal antibodies (mAbs) can be used to compare the antigenic pattern of isolates and reference strains.

Genetic Classification

Leptonema and Turneria each have one species (L. illini and T.parva, respectively), but 15 genomic species (L. interrogans, L. kirschneri, L. borgpetersenii, L. santarosai, L. noguchii, L.weilii, L.inadai, L.biflexa, L. meyeri, L. wolbachii, Genomo species 1, Genomo species 3, Genomo species 4 and Genomo species 5) have been described in the genus Leptopsira (Figure No.2). Genomic species are a class of Leptospiraceae serovars in which the related DNAs contain 5% or less unpaired bases and whose DNAs exhibit 70% or more homology at the ideal reassociation temperature of 55ºC or 60% or more homology at a strict reassociation temperature of 70ºC.

A G+C concentration of 34.4mol% is a characteristic of the genus Leptopsira. The G+C concentration of the genus Turneria is 47-48mol%, while the genus Leptonema contains 51–53mol%. On two leptospires, the whole sequencing data (serovar Lai and serovar Copenhegeni) is available. There are two chromosomes in the leptospiral genome: the giant chromosome (CI) and the tiny

chromosome (CII). The large chromosome's size spans from 4,332,241 bp to 4,277,185 bp, whereas the tiny chromosome's size falls between 358,943 bp and 350,181 bp. Despite being the gold standard method for species-level leptospire identification, DNA-DNA hybridization is rarely employed due to its complexity.

In recent years, a number of PCR-based DNA fingerprinting techniques have gained popularity and are now often employed to characterize leptospires. Among the examples are Fluorescent Amplifi ed Fragment Length Polymorphism (FAFLP), Arbitrarily Primed PCR (APPCR) and Random Amplifi ed Polymorphic DNA (RAPD) fingerprinting. Chapter 8 provides a technical description of the several methods utilized to characterize leptospires.

CLINICAL FEATURES OF LEPTOSPIROSIS

It has been said that leptospirosis is a zoonosis with variable symptoms[51,52]. To be sure, this description has been used so often that it has become cliche1. The classical description of Weil's disease merely represents the most severe presentation of the disease's incredibly wide spectrum of symptoms. In the past, it was thought that particular serogroups were linked to particular clinical disorders[53]. Nevertheless, some experts questioned this position[54-56] and more thorough research conducted over the previous 30 years has disproved this theory. The ecology of a region's maintenance animal hosts may provide an explanation for a large number of the observed relationships. More serogroup diversity will be supported by a territory with a richly varied fauna than by a zone with few animal hosts.

Icterohaemorrhagiae serogroup serovars are often, though not always, the cause of severe leptospirosis in humans. The particular serovars at play are mostly determined by the environment of the nearby maintenance hosts as well as their geographic location. Hence, serovars copenhageni and icterohaemorrhagiae, which are carried by rats, are typically to blame for infectious diseases in Europe, but serovar lai is more prevalent in Southeast Asia. Leptospirosis exhibits a biphasic clinical presentation (Figure No.3), with an approximately week-long acute or septicemic phase and an immunological phase that is marked by leptospire excretion in the urine and antibody generation[55,57,58]. The majority of leptospirosis problems arise in the second week of the illness and are linked to leptospire localization within the tissues during the immunological phase.

Specimens 1 and 2 for serology are acute-phase specimens, 3 is a convalescent-phase sample which may facilitate detection of a delayed immune response and 4 and 5 are follow-up samples which can provide epidemiological information, such as the presumptive infecting serogroup. (Adapted from reference 586a with permission of the publisher.)

Current treatment options

Leptospirosis typically manifests as mild clinical symptoms that resolve on their own[59,60]. The leptospirosis treatment protocols are directly associated with the infection's state (severity)[61-66]. For the treatment of moderate leptospirosis, oral doxycycline is typically advised. It is advised to take 100mg of doxycycline twice a day for a week in this regard. Oral administration of azithromycin (500mg/day for 3 days), ampicillin (500-750mg/day for 1 week to 10 days), and amoxicillin (500mg/day for 1 week to 10 days) is also an option[60,67-71]. The duration of the condition is shortened as a result of this therapeutic approach[72].

Apart from its therapeutic application in leptospirosis patients, doxycycline is also an antibiotic that can be given to travelers to locations that are known to be leptospirosis endemic states. Additionally, people in specific professions-such as sportsmen participating in aquatic sports and veterinarians-should use doxycycline. In this context, 200mg of oral doxycycline are given to each person once a week. The use of antibiotics should not stop while there is a chance of exposure. This antibiotic doesn't play a preventative function in preventing leptospirosis, although it may lessen its severity[73-75].

The use of antibiotics in the treatment of leptospirosis may be wise. Penicillin G (penicillin G

sodium) is given intravenously to patients suffering from severe leptospirosis, which typically presents as renal and hepatic failure (Figure No.4). Use it for a week[71,76-78]. Severe leptospirosis may also be treated with amoxicillin, ampicillin, azithromycin, doxycycline, and tetracycline, according to documented reports. Doxycycline use should be avoided by minors and expectant mothers[65,77-79]. Children and pregnant women should receive azithromycin and amoxicillin rather than doxycycline[59,60,71]. In order to preserve electrolyte and fluid homeostasis, supportive therapy is advised. In this context, individuals with severe leptospirosis have been reported to have hypomagnesemia[80,81].

Due to the high mortality rate, patients with leptospirosis who exhibit severe pulmonary signs should be closely monitored. Antimicrobial therapy should thus be given concurrently with respiratory ventilation as a mechanical therapy in order to monitor pulmonary bleeding in leptospirosis patients[72]. Apart from the antibiotics stated before, leptospirosis can also be effectively treated with cefotaxime and/or ceftriaxone[82,83]. Even though antibiotic therapy is often effective when treating leptospirosis, certain individuals may still experience Jarisch-Herxheimer responses (JHRs). JHR is a brief immunological occurrence that frequently occurs in patients receiving therapy for syphilis, leptospirosis and other spirochete diseases. Clinically, it presents as transient constitutional symptoms such fever, chills, headaches and myalgias.

The emergence of JHR was noted 24 hours following antibiotic ingestion. When it comes to the use of antibiotics to treat leptospirosis, this characteristic can be considered a global problem[84,85]. While many antibiotics can be used to treat leptospirosis, other medicines are not effective in treating leptospirosis. As a result, Leptospira species are resistant to vancomycin, rifampicin, metronidazole and chloramphenicol[86,87]. Control and prevention are significant actions that can be thought of as viable solutions to stop leptospirosis from spreading.

Promotion of hygiene and reduction of environmental contamination through the control of rodents in both zones of rural and urban areas are effective options for controlling the spread of leptospirosis and the transmission of bacterial agents of Leptospira. Simultaneously, the use of vaccines to vaccinate animals (livestock and domestic) and individuals with risky occupations is an influential preventive method in opposition to leptospirosis .The method of producing vaccines for human immunization is now making great strides. Human vaccinations have been tested in a few nations, such as China, Japan, Cuba, and France. In nations that are connected, these vaccinations are authorized for use[98-91]. Bacterins are vaccinations for humans and animals that are made by inactivating Leptospira bacteria with formalin or heat. Moreover, the outer membrane of the leptospira is used to manufacture several Chinese vaccines[89]. Therefore, leptospiral constituents, such as lipopolysaccharides (LPS) and OM proteins (OMPs), have been recognized as viable options for vaccine production. It is not possible to provide a single universal vaccine due to the considerable variability among leptospiral strains[64,71].

Furthermore, Lig proteins-which are generated during host infection-provide subunit vaccines. Bacterial adherence and escape from the human immune system are facilitated by lig proteins. The creation of a leptospirosis vaccination with good efficacy remains a challenge[92]. The pathogen has evolved defense mechanisms to evade the complement system's protective function, multiply in the blood, adhere to host cells, and enter organs and tissues more quickly[93]. The pathogen's quick colonization of several organs puts the host at serious risk, which makes the creation of a reliable leptospirosis vaccination necessary.

Vaccines that are inanimate, mainly relying on the immune response elicited by lipopolysaccharides (LPS) on their surface, usually provide a brief window of protection against the particular serovars that are included in the vaccine formulation[94]. Conversely, live-attenuated vaccines have the ability to elicit both humoral and cellular immune

responses, which can help to establish durable immunity[95]. While attenuation can adversely affect live vaccines' antigenicity, it becomes more challenging when several serovars are addressed.

Role of probiotics in the treatment of leptospirosis

More than 1014 species make up the rich and diverse microbial community found in the human gastrointestinal (GI) tract. These species interact with the host and play a major role in a number of physiological processes, most notably the support of health and development[96]. Numerous disorders, including infectious, metabolic, and noncommunicable diseases, are linked to imbalances in this gut microbiome[97,98]. It is commonly known that the gut microbiota plays a critical role in triggering, modifying, and controlling immune responses. It generates anti-inflammatory short-chain fatty acids (SCFAs), which help with cell death, tumor cell growth inhibition and mucosal barrier maintenance. The gut microbiota has a major impact on immune responses in the gut as well as other organs because of the large concentration of immune cells in the intestine[99]. New findings point to an important interaction between the lungs, liver, and kidneys-organs that are frequently linked to leptospirosis-and the gut[100,101]. Investigations exploring the function of the gut microbiota in leptospirosis infection have shown considerable changes in microbial composition following infection, specifically an increased Firmicutes/Bacteroidetes ratio[102], although the mechanisms driving this crosstalk are still largely unclear. The burden of Leptospira infections in organs increased when the gut microbiota was reduced by antibiotics; however, fecal microbiota transplantation had the reverse effect[102]. Crucially, antibiotic treatment can cause dysbiosis in the gut microbiota, even though it is intended to treat infection. This condition is marked by decreased diversity, changed abundance of certain taxa (such as some potentially harmful bacteria that become dominant, like *Clostridium perfringens*, *Staphylococcus aureus*, or *Clostridioides difficile*), altered metabolite and gene expression patterns, weakened resistance to harmful bacteria, and the emergence of microbes that are resistant to antibiotics. As a result, changes brought about by antibiotics to the gut microbiota disturb the interactions between microbes and hosts, making acute gut infections more likely[103,104]. Probiotics may be able to reduce Leptospira interrogans pathogenesis, according to a number of researches that have examined the possibility and provided information about immunomodulatory effects. Pretreatment with live Lactobacillus plantarum showed encouraging results in a murine model. Notably, repeated oral administration of L. plantarum reduced histopathological disease symptoms, adjusted the inflammatory response, and returned diseased mice to normal body weight[105]. Analysis showed changes in immune cell profiles, including postinfection shifts toward effector CD4+ helper T cells and increases in B-cell and CD4+ helper T-cell populations. Additionally, pretreatment increased the numbers of macrophages and monocytes in lymphoid regions, which may have coordinated a multifaceted response including T-cell and myeloid subsets. Immunohistochemistry showed that kidney sections from pretreatment infected mice had an enrichment of neutrophils and macrophages, which was associated with a decrease in leucocyte and T-cell infiltration. This finding raises the possibility of a link between these cellular responses and a reduction in pathogenesis.

A different study looked into the immunomodulatory properties of Saccharomyces boulardii, a probiotic that is known to increase immune cell activity and the production of anti-inflammatory cytokines. S. boulardii significantly elevated IL-10 expression and antibody titres in conjunction with DNA vaccines encoding leptospiral protein fragments, especially with pTARGET/ligBrep immunization. These results provide a unique approach to boost vaccine efficacy by pointing to a possible function for S. boulardii in augmenting humoral immune responses linked to DNA vaccination. Additionally, it has been demonstrated that different Leptospira serogroups are antagonistically affected by strains of Bacillus

subtilis[106]. These strains produced bacteriocins and enzymes that caused several Leptospira strains to lyse, which may have uses in veterinary care and environmental cleaning to fight leptospirosis.

Antibiotic-associated gut microbiota dysbiosis may be prevented or treated using probiotic microorganisms and nutritional supplements. Nevertheless, Hungarian scientists' thorough systematic review and meta-analysis concluded that probiotic administration is not recommended during antibiotic therapy in order to prevent low-diversity dysbiosis[107]. Probiotics did not appear to have a discernible impact on preserving diversity, according to the meta-analysis of Shannon, Chao1, and observed OTU diversity indices[107].

Corticosteroids in severe leptospirosis

There are two main phases to leptospirosis, a potentially serious zoonotic illness[108]. Acute febrile bacteremia characterizes the first phase, which is followed by a period of apparent recovery. But the next phase, known as the "immune" phase, is characterized by a return of fever and the appearance of problems. Five to fifteen percent of patients develop Weil's illness, which frequently manifests as lung involvement, including Acute Respiratory Distress Syndrome[109-111]. There were two systematic reviews found, one with a meta-analysis[112,113]. Four researches were given in a qualitative synthesis in the first review by[114]. However, the absence of information on the search procedure raises questions about the possibility that significant research were overlooked, which could have an impact on the validity of their conclusions. The validity of their conclusions is further undermined by the small number and low quality of research, as well as the lack of explicit inclusion criteria for study type, participants, intervention, and end measures. The characterization of pulmonary involvement and the uniformity of corticosteroid treatment regimens presented difficulties for both comprehensive evaluations. Nosocomial infection rates may have increased as a result of dosage differences, such as the high amount of dexamethasone employed in one trial compared to methylprednisolone in another. The interpretation of outcomes is further complicated by differences in the frequency, duration, and concurrent drugs of treatment[114]. proposed the advantages of early methylprednisolone administration for severe leptospirosis patients with pulmonary problems, although offering scant evidence and recommendations. This is in contrast to the results of[116], who found no differences in the therapeutic effects between early high-dose ($p \geq 0.05$; 95% CI: 0.81-1.37), early low-dose ($p \geq 0.05$; 95% CI: 0.3-1.03) and late low-dose ($p \geq 0.05$; 95% CI: 0.11-2.52) corticosteroids. Despite the fact that[116] provided a more thorough synthesis of randomized controlled trials, there are still issues that need to be resolved for continued progress, including the small number of studies and substantial statistical heterogeneity. In conclusion, there is still little data supporting the use of high-dose corticosteroids in treating patients with severe leptospirosis who have pulmonary problems. It is necessary to conduct more carefully planned RCTs with big enough sample numbers. Future research on this subject must pay close attention to methodological issues, such as the characterization of disease severity, uniformity of treatment, and consistency of outcome measurement**.**

FUTURE DIRECTIONS

Future study is needed to establish whether leptospirosis patients are likely to develop severe disease, as there are presently no trustworthy scoring systems or predictive models in place for this purpose. Since there is little knowledge about the pathophysiology of severe leptospirosis, fundamental sciences research should concentrate on finding possible treatment targets and biomarkers of severity. More randomized studies are needed to assess possibly helpful therapies that might stop the onset of severe disease[115].

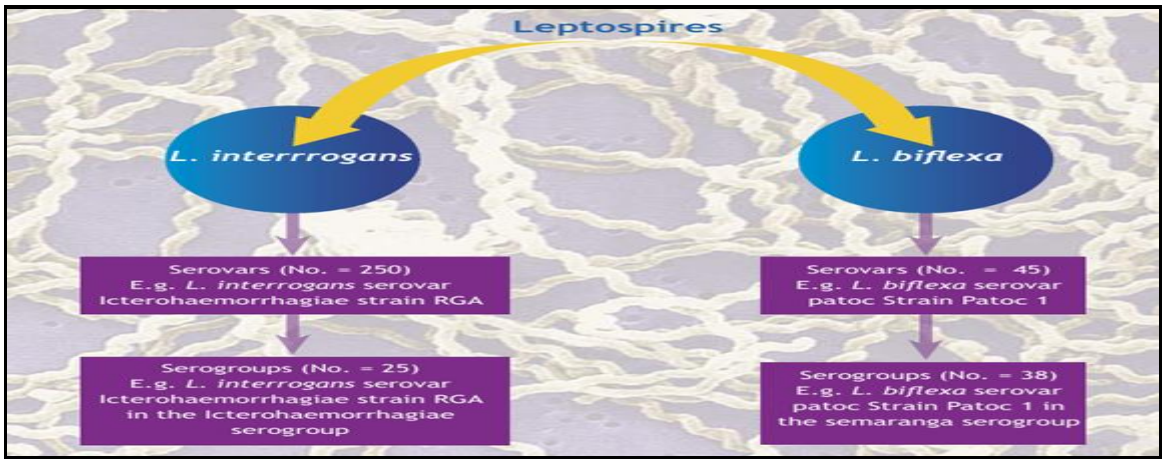

Figure No.1: Phenotypic Classification

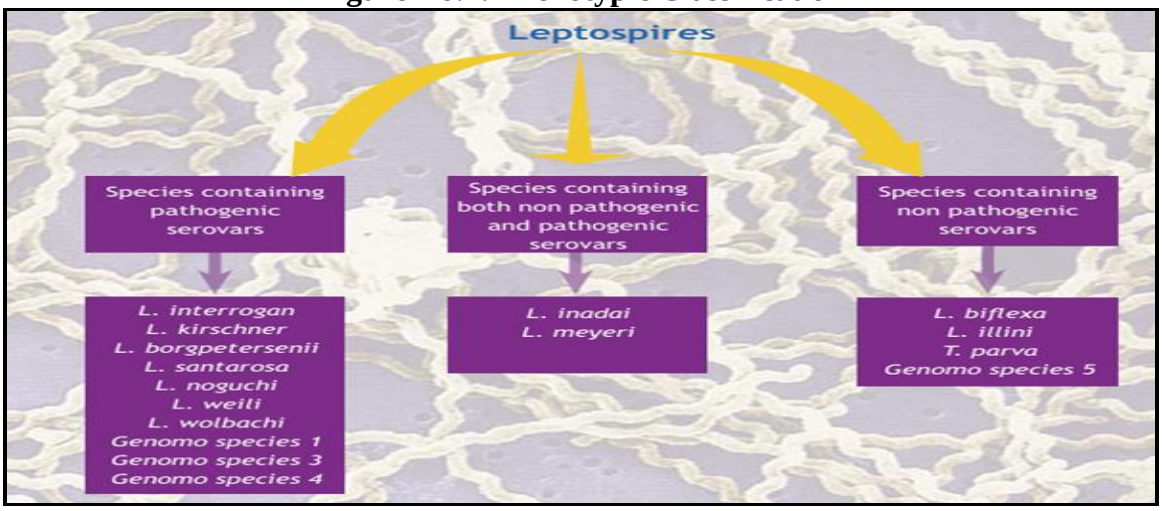

Figure No.2: Genotypic Classification

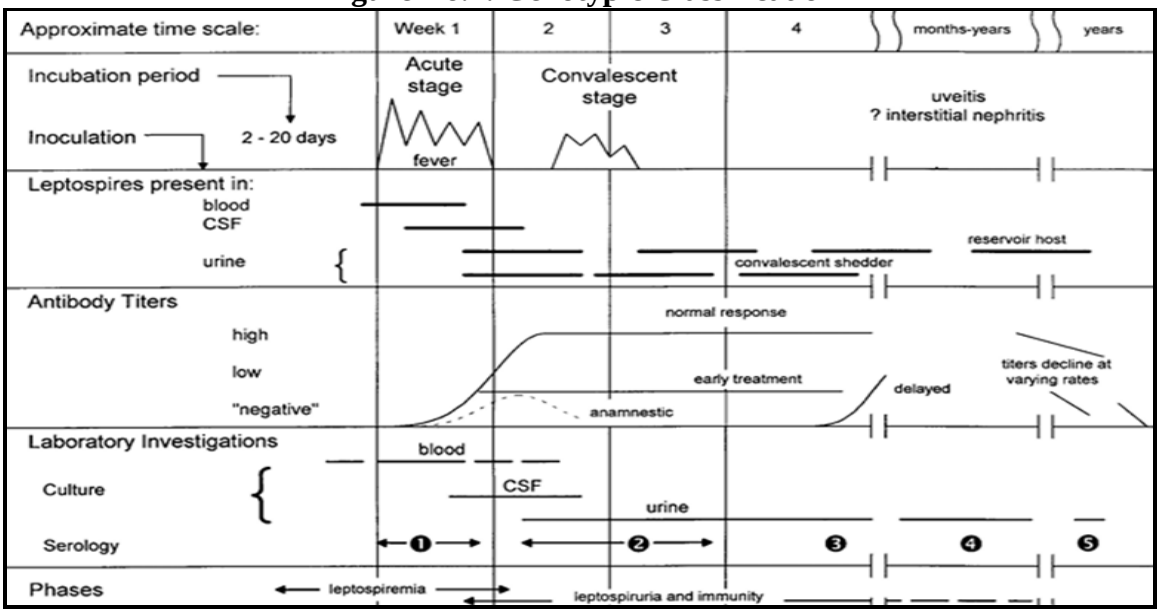

Figure No.3: Biphasic nature of leptospirosis and relevant investigations at different stages of disease

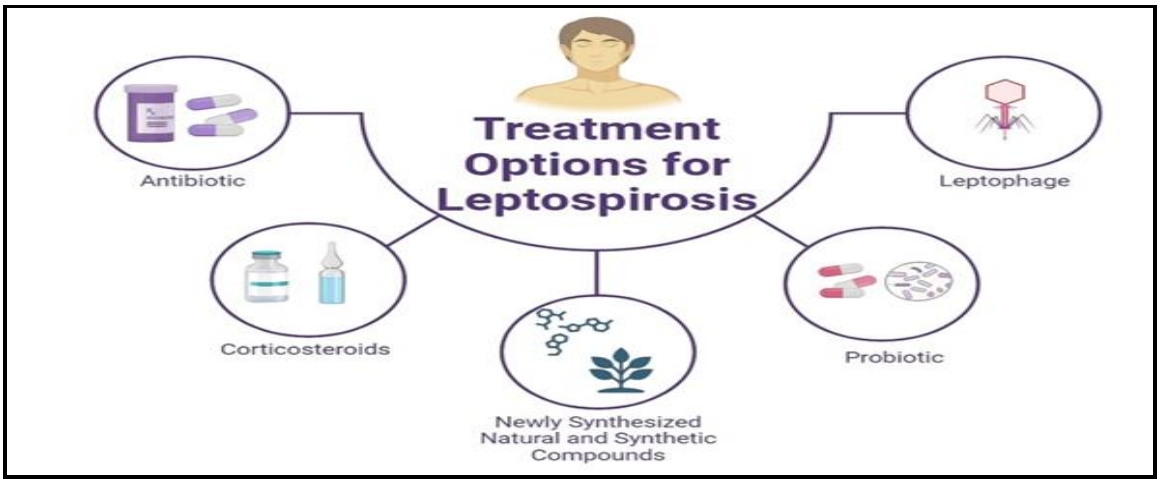

Figure No.4: Current Treatment Options

CONCLUSION

Effective preventative measures have been developed as a result of years of understanding the epidemiology and etiology of leptospirosis. Leptospirosis is still a disease that has a significant economic impact on animal husbandry in affluent nations, although the majority of human disease cases occur in tropical and subtropical developing nations. Leptospirosis outbreaks in the past few years have brought attention to the possible impacts of human activity and climate change on the disease's incidence and wide range of clinical presentations. Early anti-biotic medication initiation is crucial in acute sickness and this understanding has led to the development of various promising quick diagnosis methods. However, the need for more straightforward tests that can be used many of these diagnostic advancements, meanwhile, will not be available to the populations that would benefit from them the most. Although our knowledge of the pathogenesis mechanisms is still lacking on a more fundamental level, new developments in the molecular biology of leptospires provide hope for future research to go more quickly.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Buddha Institute of Pharmacy, Gida, Gorakhpur, Uttar Pradesh, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Waitkins S A. Leptospirosis In: Manson's tropical diseases, *Eds. Manson-Bhor PEC, Bell DR. London, Bailliére Tindall*, 19th Edition, 1987, 657-665.
2. Tangkanakul W, Tharmaphornpil P, Plikaytis BD, Bragg S, Poonsuksombat D, Choomkasien P, Kingnate D, Ashford D A. Risk factors associated with leptospirosis in Northeastern Thailand, *Am J Trop Med Hyg*, 63(3-4), 2000, 204-208.
3. Smythe L D, Field H E, Barnett L J, Smith C S, Dohnt M F, Symonds M L, Moore M R, Rolfe P F. Leptospiral antibodies in flying foxes in Australia, *J Wildl Dis*, 38(1), 2002, 182-186.
4. Zaki S R, Sheih W J. Leptospirosis associated with outbreak of acute febrile illness with pulmonary haemorrhage, Nicaragua, The epidemic working group at Ministry of Health in Nicaragua, *Lancet*, 347(9000), 1996, 535-536.
5. Ko A I, Reis M G, Dourado C M R, Johnson Jr. W D, Riley L W. Salvador Leptospirosis Study Group, Urban epidemic of severe leptospirosis in Brazil, *The Lancet*, 354(9181), 1999, 820-825.

6. Barcellos C, Sabroza P C. The place behind the case: leptospirosis risk and associated environmental conditions in a flood-related outbreak in Rio de Janeiro, *Cad Saude Publica, Rio de Janeiro,* 17, 2001, 59-67.
7. World Health Organization. Leptospirosis, India - report of the investigation of a post-cyclone outbreak in Orissa, November, *Wkly Epidemiol Rec*, 75(27), 2000, 217-223.
8. Sehgal S C, Sugunan A P, Vijayachari P. Outbreak of leptospirosis after cyclone in Orissa, *National Med J India,* 15(1), 2001, 22-23.
9. Karande S, Kulkarni H, Kulkarni M, De A, Varaiya A. Leptospirosis in children in Mumbai slums, *Indian J Pediatr,* 69(10), 2002, 855-858.
10. Sehgal S C, Murhekar M V, Sugunan A P. Outbreak of leptospirosis with pulmonary involvement in North Andaman, *Indian J Med Res,* 102, 1995, 9-12.
11. Singh S S, Vijayachari P, Sinha A, Sugunan A P, Rashid M A, Sehgal S C. Clinico-epidemiological study of hospitalized cases severe leptospirosis, *Indian J Med Res,* 109, 1999, 94-99.
12. Faine S. Guidelines for control of leptospirosis, *World Health Organization, Geneva,* 67, 1982, 1-171.
13. Levett P N. Leptospirosis, *Clin Microbiol Rev*, 14(2), 2001, 296-326.
14. Silvia R R V, Brauner J S. Leptospirosis as a cause of acute respiratory failure: Clinical features and outcome in 35 critical care patients, *Brazilian J Infect Dis,* 6(3), 2002, 135-139.
15. Ramachandran S, Perera M V F. Cardiac and pulmonary involvement in leptospirosis, *Trans Royal Soc Trop Med Hyg,* 71(1), 1977, 56-59.
16. Muthusethupathy M A, Sivakumar S, Vijayakumar R, Jayakumar M. Renal involvement in leptospirosis – our experience in Madras city, *J Post Graduate Med (India),* 40(3), 1994, 127-131.
17. Rathinamsivakumar, Ratnam S, Sureshbabu L, Natarajaseenivasan K. Leptospiral antibodies in patients with recurrent ophthalmic involvement, *Indian J Med Res,* 103, 1996, 66-68.
18. Rathinam S R, Rathnam S, Selvaraj S, Dean D, Nozik R A, Namperumalsamy P. Uveitis associated with an epidemic outbreak of leptospirosis, *Am J Ophthalmol,* 124(1), 1997, 71-79.
19. Oh H B, Chang W H, Cho M K, Seong W K, Park K S. Identifi cation of new serovars yeonchon and hongchon belonging to Leptospira interrogans of the Icterohaemorrhagiae serogroup, *J. Korean Soc Microbiol,* 26(3), 1991, 253-262.
20. Simpson F G, Green K A, Haug G J, Brookes D L. Leptospirosis associated with severe pulmonary haemorrhage in Far North Queensland, *Med J Aust,* 169(3), 1999, 151-153.
21. Zeurner R L, Bolin C A. Differentiation of Leptospira interrogans isolates by Is1500 hybridization and PCR assays, *J Clin Microbiol,* 35(10), 1997, 2612-2617.
22. Trefejo R T, Rigau-Perez J G, Ashford D A *et al*. Epidemic leptospirosis associated with pulmonary haemorrhage – Nicaragua, *J Infect Dis,* 178(5), 1998, 1457-1463.
23. Vijayachari P, Sehgal S C, Goris M G A, Terpstra W J, Hartskeerl R A. Leptospira interrogans serovar Valbuzzi: A case of severe pulmonary haemorrhages in Andaman Islands, *J Med Microbiol,* 52(Pt2), 2003, 913-918.
24. Weil A. Uebereineeigenthümliche, mitMilztumor, icterus and nephritis einhergehende, acute infectionsskrankheit, *Dtsch Arch Klin Med,* 39, 1886, 209.
25. Faine S, Alder B, Bolin C, Perolat P. Leptospira and Leptospirosis, Melbourne, Australia, *MediSci,* 1999.
26. Faine S. Leptospira and Leptospirosis, *CRC Press, London,* 1994.

27. Stimson A M. Note on an organism found in yellow-fever tissue, *Pub Hlth Rep,* 22(18), 1907, 541.
28. Abdussalam M, Alexander A D, Babudieri B, Borg-Peterson C, Eichhorn E A, Galton M M, Kaplan M M, Stableforth A W, Turner L H, Van Der Hoeden J, Wolff J W, Yager R H. Classifi cation of leptospires and recent advances in leptospirosis, *Bull Wrld Hlth Org,* 32(6), 1965, 881-891.
29. Baker M F, Baker H J. Pathogenic leptospires in Malaysian surface waters I, A method of survey for leptospira in natural waters and soils, *Am J Trop Med Hyg,* 19(3), 1970, 485-492.
30. Kmety E, Dicken H. Revised list of "Leptospira" serovars, I Alphebetical order, II chronological order, 1 and 2, Griningen, *University Press, Netherlands,* 1988.
31. Kmety E, Dicken . Classifi cation of the species Leptospira interrogans and history of its serovars. Griningen, *University Press, Netherlands,* 1993, 104.
32. Ellis W A, Logan E F, O'Brien J J, Neill S D, Ferguson H W, Hanna J. Antibodies to leptospira in the sera of aborted bovine foetuses, *Vet Rec,* 103(11), 1978, 237-239.
33. Ellis W A, O'Brien J J, Cassells J. Role of cattle in the maintenance of Leptospira interrogans serotype hardjo infection in Northern Ireland, *Vet Rec,* 108(26), 1981, 555-557.
34. Ellis W A, McParland P J, Bryson D G, McNulty M S. Leptospires in pig urogenital tract and foetuses, *Vet Rec,* 117(3), 1985, 66-67.
35. Terpstra W J, Ligthart G S, Schoone G J. ELISA for the detection ospecifi cIgM and IgG in human leptospirosis, *J Gen Microbiol,* 131(2), 1985, 377-385.
36. Chowdry A K. Jaundice at Port Blair, Andaman Islands, *Indian Med. Gaz,* 38(11), 1903, 409 -412.
37. Taylor J, Goyle A N. Leptospirosis in Andamans, Indian Medical Research Memoirs, (Memoir No. 20), *Ind. J. Med. Researdh,* 1931.
38. Woolley J M. Malaria in Andamans, *Indian Med. Gaz,* 48(7), 1913, 266-267.
39. De Castro A B. Toxic Jaundice of unknown origin, *Indian Med. Gaz,* 57(8), 1922, 292.
40. Dasgupta B M, Chopra R N. The occurrence of Weil's disease in India, *Indian Med. Gaz,* 72(10), 1937, 610-612.
41. Dasgupta B M. A note upon an interesting serological type of leptospira in the Andamans, *Indian Med. Gaz,* 74(2), 1939, 88-89.
42. Dalal P M. Leptospirosis in Bombay: Report of five cases, *Indian J. Med. Sci,* 14, 1960, 295-301.
43. Muthusethupathy M A, Sivakumar S. Acute renal failure due to leptospirosis, *J. Asso. Phy, India,* 35(9), 1987, 631-635.
44. Muthusethupathy M A, Sivakumar S, Suguna Rajendar, Vijayakumar R, Jyaykumar M. Leptospiral renal failure in Madras city, *Indian J. Nephro – News Series,* 1, 1991,15-16.
45. Ramachandran S, Perera M V F. Cardiac and pulmonary involvement in leptospirosis, *Trans. Royal Soc. Trop. Med. Hyg,* 71(1), 1977, 56-59.
46. Johnson R C, Harris V G. Differentiation of pathogenic and saprophytic leptospires: 1 growth at low temperature, *J Bacteriol,* 94(1), 1967, 27-31.
47. Johnson R C, Rogers P. Differentiation of pathogenic and saprophytic leptospires with 8-Azaguanine, *J. Bacteriol,* 88(6), 1964, 1618-1623. Noel R. Krieg. The spirochetes in Bergey's manual of systematic bacteriology, *John G. Holt, Williams and Wilkins, London,* 1, 1984, 39-70.
48. International Committee on Systematic Bacteriology, Sub Committee on the Taxonomy of Leptopsira, Minutes of the meeting, 5-6 September, 1986 Manchester, England, *Intl. J. Sys Bacteriol,* 1987, 472-473.

49. Brenner D J, Kaufmann A F, Sulzer K R, Steigerwalt A G, Rogers F C, Weyant R S. Further determination of DNA relatedness between serogroups and serovars in the family Leptospiraceae with a proposal for Leptospira alexanderi sp. nov and four new Leptospira genomospecies, *Int J Syst Bacteriol*, 49(Pt2), 1999, 839-858.
50. Kmety E and Dikken H. Classification of the species Leptospira interrogans and history of its serovars, *University Press Groningen, The Netherlands*, 1993, 104.
51. Peter G. Leptospirosis: A zoonosis of protean manifestations, *Pediatr. Infect. Dis. J*, 1(4), 1982, 282-288.
52. Woodward T. The protean mainfestations of leptospirosis, In Symposium on the leptospirosis, U*.S. Government Printing Office, Washington, D.C*, 1953, 57-68.
53. Van Thiel P H. The leptospirosis, *University of Leiden, Leiden, The Netherlands*, 1948.
54. Alexander A D, Benenson A S, Byrne R J, Diaz-Rivera R S, Evans L B, Gochenour W S, Hall H E, Hightower J A, Jeffries H, De Jesu's J, Martinez E, Paniagua M, Pons J A, Ramos-Morales F, Rodri-guez-molina R, Swisher K Y, Woodward T E, Yager R H. Leptospirosis in Puerto Rico, *Zoonoses Res*, 2, 1963, 152-227.
55. Edwards G A, Domm B M. Human leptospirosis, *Medicine*, 39, 1960, 117-156.
56. Feigin R D, Anderson D C. Human leptospirosis, *Crit. Rev. Clin. Lab. Sci*, 5(4), 1975, 413-467.
57. Kelley P W. Leptospirosis, In S. L. Gorbach, J. G. Bartlett, N. R. Blacklow (ed.), Infectious diseases, *W. B. Saunders, Philadelphia*, 2nd Edition, 1998, 1580-1587.
58. Turner L H. Leptospirosis I, *Trans. R. Soc. Trop. Med. Hyg*, 61(6), 1967, 842-855.
59. Haake D A, Levett P N. Leptospirosis in humans, *Leptospira Leptospir*, 387, 2015, 65-97.
60. Chacko C S, Jayakumar A, Binu S L, Pant R D, Giri A, Chand S, *et al*. A short review on leptospirosis: Clinical manifestations, diagnosis and treatment, *Clin Epidemiol Global Health*, 11, 2021, 100741.
61. Monahan A, Miller I, Nally J. Leptospirosis: risks during recreational activities, *J. Appl. Microbiol*, 107(3), 2009, 707-716.
62. Lucheis S, Ferreira R. Ovine leptospirosis in Brazil, *J Venom Anim Toxins Incl. Trop Dis*, 17(4), 2011, 394-405.
63. Klaasen H, Van Der Veen M, Sutton D, Molkenboer M. A new tetravalent canine leptospirosis vaccine provides at least 12 months immunity against infection, *Vet. Immunol. Immunopathol*, 158(1-2), 2014, 26-29.
64. Grassmann A A, Souza J D, McBride A J A. A universal vaccine against leptospirosis: Are we going in the right direction? *Front. Immunol*, 8, 2017a, 256.
65. Gopi C, Sri C S, Krupamai G, Magesh A R, Dhanaraju M D. Recent progress in the treatment of leptospirosis, *SN Comprehens Clin Med*, 3(4), 2021, 1018-1025.
66. McClain J B L, Ballou W R, Harrison S M, Steinweg D L. Doxycycline therapy for leptospirosis, *Ann. Intern. Med*, 100(5), 1984, 696-698.
67. Hospenthal D R, Murray C K. *In vitro* susceptibilities of seven Leptospira species to traditional and newer antibiotics, *Antimicrob. Agents Chemother*, 47(8), 2003, 2646-2648.
68. Pappas G, Cascio A. Optimal treatment of leptospirosis: Queries and projections, *Int. J. Antimicrob. Agents*, 28(6), 2006, 491-496.
69. Charan J, Saxena D, Mulla S, Yadav P. Antibiotics for the treatment of leptospirosis: Systematic review and meta-analysis of controlled trials, *Int. J. Prev. Med*, 4(5), 2013, 501-510.
70. Kumar S S. Indian guidelines for the diagnosis and management of human leptospirosis in Medicine Update, *Ed. A. Muruganathan (Bhopal, India: API India)*, 2013, 23-29.

71. Karpagam K B, Ganesh B. Leptospirosis: A neglected tropical zoonotic infection of public health importance-an updated review, *Eur. J. Clin. Microbiol. Infect. Dis,* 39(5), 2020, 835-846.
72. Fraga T R, Carvalho E, Isaac L, Barbosa A S. Leptospira and leptospirosis, *Molecular Medical Microbiology, (Amsterdam: Academic Press),* 3rd Editionn, 2024, 1849-1871.
73. Takafuji E T, Kirkpatrick J W, Miller R N, Karwacki J J, Kelley P W, Gray M R, *et al*. An efficacy trial of doxycycline chemoprophylaxis against leptospirosis, *N. Engl. J. Med*, 310(8), 1984, 497-500.
74. Gonsalez C R, Casseb J, Monteiro F G, Paula-Neto J B, Fernandez R B, Silva M V. Use of doxycycline for leptospirosis after high-risk exposure in São Paulo, *Brazil. Rev. Inst. Med. Trop. Sao Paulo,* 40(1), 1998, 59-61.
75. Sehgal S, Sugunan A, Murhekar M, Sharma S, Vijayachari P. Randomized controlled trial of doxycycline prophylaxis against leptospirosis in an endemic area, *Int. J. Antimicrob. Agents,* 13(4), 2000, 249-255.
76. Watt G, Tuazon M L, Santiago E, Padre L, Calubaquib C, Ranoa C. Placebo-controlled trial of intravenous penicillin for severe and late leptospirosis, *Lancet,* 1(8583), 1988, 433-435.
77. Griffith M E, Hospenthal D R, Murray C K. Antimicrobial therapy of leptospirosis, *Curr. Opin. Infect. Dis,* 19(6), 2006, 533-537.
78. Jamal Khan S, Bilal Khattak M, Khan A. Leptospirosis: A disease with global prevalence, *J Microbiol Exp,* 6(5), 2018, 219-221.
79. Guzman Perez M, Blanch Sancho J J, Segura Luque J C, Mateos Rodriguez F, Martinez Alfaro E, Solís Garcia Del Pozo J, *et al*. Current evidence on the antimicrobial treatment and chemoprophylaxis of human leptospirosis: A meta-analysis, *Pathogens,* 10(9), 2021, 1125.
80. Craig S B, Graham G C, Burns M A, Dohnt M, Jansen C, Smythe L D, *et al*. Hypomagnesaemia in the first 10 days of severe leptospirosis, *Ann. Trop. Med. Parasitol,* 103(8), 2009, 705-709.
81. Panaphut T, Domrongkitchaiporn S, Vibhagool A, Thinkamrop B, Susaengrat W. Ceftriaxone compared with sodium penicillin G for treatment of severe leptospirosis, *Clin. Infect. Dis*, 36(12), 2003, 1507-1513.
82. Suputtamongkol Y, Niwattayakul K, Suttinont C, Losuwanaluk K, Limpaiboon R, Chierakul W, *et al*. An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis, *Clin. Infect. Dis,* 39(10), 2004, 1417-1424.
83. Friedland J S, Warrell D A. The Jarisch-Herxheimer reaction in leptospirosis: Possible pathogenesis and review, *Rev. Infect. Dis*, 13(2), 1991, 207-210.
84. Dhakal A, Sbar E. Jarisch Herxheimer reaction, *Treasure Island (Florida): Stat Pearls Publishing*, 2022.
85. Faine S, Adler B, Bolin C, Perolat P. Leptospira and leptospirosis, Melbourne, *MediSci, Australi*, 1999.
86. Morgan L K. Fatal leptospirosis presenting as musculoskeletal pain, *Med. J. Aust,* 180(1), 2004, 29-31.
87. Sanchez R M, Sierra A P, Am O F, Gonzalez I R, Gil A B, Suarez M B, *et al*. Reactogenecity and immunogenecity of Cuban trivalent inactivated vaccine against human leptospirosis in different vaccination schedules, *Rev. Cubana Med. Trop,* 54(1), 2002, 37-43.
88. Yan Y, Chen Y, Liou W, Ding J, Chen J, Zhang J, *et al*. An evaluation of the serological and epidemiological effects of the outer envelope vaccine to leptospira, *J. Chin. Med. Assoc*, 66(4), 2003, 224-230.
89. Martinez R, Perez A, Cruz R, Alvarez A, Armesto M, Fernandez C, *et al*. Efficacy and safety of a vaccine against human

leptospirosis in Cuba, *Pan Am. J. Public Health*, 15(4), 2004, 249-255.
90. Yanagihara Y, Villanueva S Y, Yoshida S, Okamoto Y, Masuzawa T. Current status of leptospirosis in Japan and Philippines, *Comp. Immunol. Microbiol. Infect. Dis,* 30(5-6), 2007, 399-413.
91. Williams R B, Gobbi L. Comparison of an attenuated anticoccidial vaccine and an anticoccidial drug programme in commercial broiler chickens in Italy, *Avian Pathol,* 31(3), 2002, 253-265.
92. Koizumi N, Watanabe H. Leptospirosis vaccines: Past, present and future, *J. Postgrad. Med,* 51(3), 2005, 210-214.
93. Wang Z, Jin L, Wegrzyn A. Leptospirosis vaccines, *Microb. Cell Fact,* 6, 2007, 39.
94. Bashiru G, Bahaman A R. Advances and challenges in leptospiral vaccine development, *Indian J. Med. Res,* 147(1), 2018, 15-22.
95. Honda K, Littman D R. The microbiota in adaptive immune homeostasis and disease, *Nature,* 535(7610), 2016, 75-84.
96. Noce A, Marrone G, Di Daniele F, Ottaviani E, Wilson Jones G, Bernini R, *et al*. Impact of gut microbiota composition on onset and progression of chronic noncommunicable diseases, *J. Nutr,* 11(5), 2019, 1073.
97. Ancona G, Alagna L, Alteri C, Palomba E, Tonizzo A, Pastena A, *et al*. Gut and airway microbiota dysbiosis and their role in COVID-19 and long-COVID, *Front. Immunol,* 14, 2023, 1080043.
98. Tripathi A, Debelius J, Brenner D A, Karin M, Loomba R, Schnabl B, *et al*. The gut–liver axis and the intersection with the microbiome, *J Nat Rev Gastroenterol Hepatol,* 15(7), 2018, 397-411.
99. Bingula R, Filaire M, Radosevic-Robin N, Bey M, Berthon J Y, Bernalier-Donadille A, *et al*. Desired turbulence? Gut-lung axis, immunity and lung cancer, *J. Oncol,* 2017, 1-15.
100. Petakh P, Isevych V, Kamyshnyi A, Oksenych V. Weil's disease Immunopathogenesis, multiple organ failure and potential role of gut microbiota, *Biomol. Ther,* 12(12), 2022a, 1830.
101. Xie X, Liu J, Chen X, Zhang S, Tang R, Wu X, *et al*. Gut microbiota involved in leptospiral infections, *ISME J,* 16(3), 2022, 764-773.
102. Strati F, Pujolassos M, Burrello C, Giuffre M R, Lattanzi G, Caprioli F, *et al*. Antibiotic-associated dysbiosis affects the ability of the gut microbiota to control intestinal inflammation upon fecal microbiota transplantation in experimental colitis models, *Microbiome,* 9(1), 2021, 39.
103. Duan H, Yu L, Tian F, Zhai Q, Fan L, Chen W. Antibiotic-induced gut dysbiosis and barrier disruption and the potential protective strategies, *Crit. Rev. Food Sci. Nutr,* 62(6), 2022, 1427-1452.
104. Potula H H, Richer L, Werts C, Gomes-Solecki M. Pre-treatment with Lactobacillus plantarum prevents severe pathogenesis in mice infected with Leptospira interrogans and may be associated with recruitment of myeloid cells, *PLoSNegl. Trop. Dis,* 11(8), 2017, e0005870.
105. Elias A J, Barna V, Patoni C, Demeter D, Veres D S, Bunduc S, *et al*. Probiotic supplementation during antibiotic treatment is unjustified in maintaining the gut microbiome diversity: A systematic review and meta-analysis, *BMC Med,* 21(1), 2023, 262.
106. Neustroev M P, Stepanova A M, Parnikova S I, Petrova S G, Zhirkov A D, *et al*. Bactericidal action of the Bacillus subtilis bacterial strains on the agents of leptospirosis, *Russ. Agric. Sci*, 41, 2015, 403-405.
107. Xavier V, Baby B, George J M, Ittyachen A M. COVID-19 and leptospirosis, pulmonary involvement and response to steroids: A comparative observational study from a rural tertiary care center in Kerala, *J. Family Med. Prim. Care,* 11(1), 2022, 294-298.

108. Vieira S R. Leptospirosis as a cause of acute respiratory failure: Clinical features and outcome in 35 critical care patients, *Braz. J. Infect. Dis*, 6(3), 2002, 135-139.
109. Dolhnikoff M, Mauad T, Bethlem E P, Carvalho C R R. Pathology and pathophysiology of pulmonary manifestations in leptospirosis, *Braz. J. Infect. Dis,* 11(1), 2007, 142-148.
110. Gulati S, Gulati A. Pulmonary manifestations of leptospirosis, *Lung India,* 29(4), 2012, 347-353.
111. Rodrigo C, Lakshitha De Silva N, Goonaratne R, Wijesinghe I. High dose corticosteroids in severe leptospirosis: A systematic review, *Trans. R. Soc. Trop. Med. Hyg,* 108(12), 2014, 743-750.
112. Rodriguez-Gonzalez I, Fillonneau C, Blanchet B, Suard I, Catilina P, Andre-Fontaine G. Efficacy of Spirolept vaccine against human leptospirosis as estimated by passive protection of laboratory rodents, *Med. Mal. Infect*, 34(5), 2004, 196-200.
113. Duggal A, Ganapathy A, Ratnapalan M, Adhikari N K. Pharmacological treatments for acute respiratory distress syndrome: Systematic review, *Minerva Anestesiol,* 81(5), 2015, 567-588.
114. Rajapakse S, Rodrigo C, Handunnetti S M, Fernando S D. Current immunological and molecular tools for leptospirosis: Diagnostics, vaccine design and biomarkers for predicting severity, *Ann Clin Microbiol Antimicrob,* 14, 2015, 2.
115. Sehgal S C. Leptospirosis on the horizon, *National Medical Journal of India,* 13(5), 2000, 228-230.
116. Spichler A, Athanazio D A, Furtado J, Seguro A, Vinetz J M. Case report: Severe, symptomatic hypomagnesemia in acute leptospirosis, *Am. J. Trop. Med. Hyg,* 79(6), 2008, 915-917.

Please cite this article in press as: Saumya Srivastava *et al*. A review on leptospirosis, *Asian Journal of Phytomedicine and Clinical Research,* 11(4), 2023, 82-98.