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### RESEARCH ARTICLE

#### A REVIEW ON EPIDEMIOLOGY, PATHOGENESIS AND TREATMENT OF LEPTOSPIROSIS

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#### Abstract

Leptospirosis is a zoonotic disease, it arises worldwide but it is most frequent in tropical and subtropical zone. It is one of the notifiable and treatable disease. Leptospirosis is a plague caused by species of bacteria called *Leptospira*; the bacteria shed into the nature via urine of infected animals. Rats are the most recurrent source of human sepsis. Rivers are the assumption to be a predominant risk factor for transmission of disease to humans. It possesses an extensive variation of mechanisms that allow them to avoid the host immune system and cause infection. The infection is extremely vast ranging from subclinical to multi organ infection with elevated mortality. It is frequently mild but can be terminal, it is likely to be serious and the serious alignment form known as Weil's disease and can easily steer to death. The mingling of renal failure, hemorrhage and jaundice is known as Weil's disease. It is the most affection pattern associated with critical leptospirosis. It is accumulating as a serious problem worldwide and superficially existing as co-infections with various unrelated diseases, including malaria and dengue. Laboratory diagnostic tests are not always accessible and usually diagnosis is executed by enzyme linked immunosorbent assay (ELISA); serology and microscopic agglutination test, rapid test are also feasible. The MAT (microscopic agglutination test) is known as "Gold standard". Serological tests are most frequently used for the diagnosis of leptospirosis. The carcinogenesis of human disease and mechanism of cell membrane injuries which take place mainly due to the occupancy of leptospirosis along with their antigen in host tissues; many molecules hand out to the ability of leptospira to invade, colonize and to adhere. In most of the cases antibiotics are preferred to reduce the symptoms of leptospirosis.

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#### Introduction:-

Leptospirosis is a re-emerging disease caused by a gram negative bacterium. It belongs to the phylum spirochetes, family-leptospiraceae and genus leptospira<sup>5</sup>. Mostly infectious diseases like the leptospirosis caused by a wide variety of pathogens like bacteria, fungi, and viruses. Approximately 500,000 of high risk cases occur globally with fatality rate 30% per annum<sup>6</sup>. Leptospirosis is an important public health problem with significant morbidity and mortality. In young and middle aged men the incidence is more than compared older men and women<sup>11</sup>. Humans can procure this infection through the exposure of wound or mucous membrane to bacteria. Sometimes the exposure can occur through direct or indirect contact. Direct contact through animal's indirect contact through the exposure to

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water that has been contaminated by the urine of some infected animals. Animals like cows, pigs, dogs, buffaloes can carry leptospira in their kidneys during an infection<sup>2</sup>.



Fig-1 leptospira<sup>18</sup>

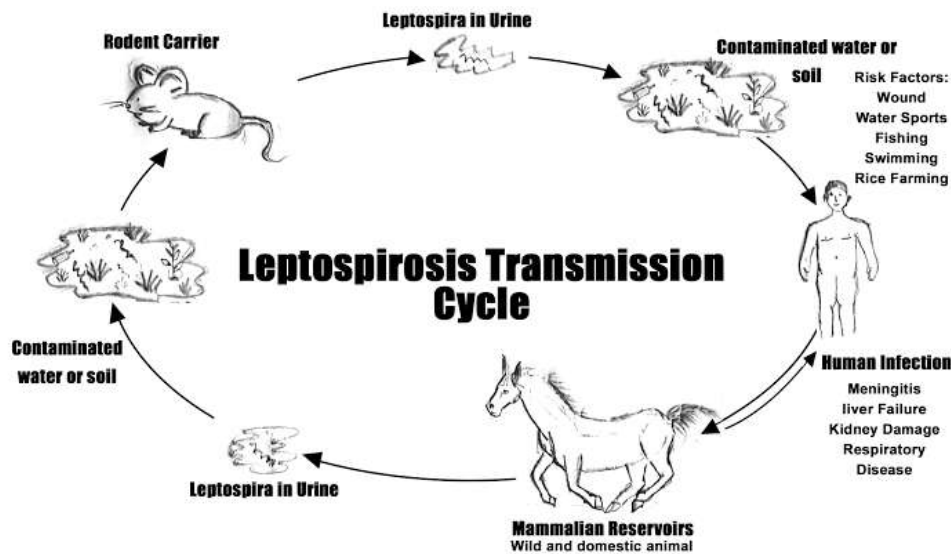


Fig 2:- Transmission Cycle of leptospirosis<sup>16</sup>

Leptospira is invaded into body through skin lesion and also by contact with wet skin or sometimes by inhalation and other surface proteins. It also affects endothelium of small vessels and cause ischemic damages in organs like kidneys, liver, lungs, and muscles. In some cases thrombocytopenia may also occur<sup>5</sup>. Leptospirosis has been elucidated into three forms ranging from milder anicteric icteric and severe Weil's disease. These cause multi organ failure<sup>11</sup>. The microbiological methods or serology are the definitive diagnosis of leptospirosis. Treatment for leptospirosis depends on severity of queasiness at presentation. Clinical presentation can vary in severity from asymptomatic to multi-organ failure<sup>11</sup>. The primary serological tests and MAT are the possible diagnosis for leptospirosis<sup>5</sup>. Hence leptospirosis is 10 times more prevalent in tropical climates compared to pleasant climates<sup>9</sup>.

### Epidemiology:-

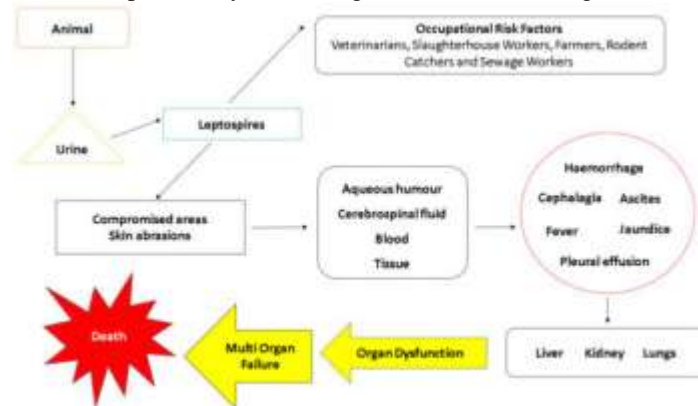
The epidemiology of leptospirosis and ecology of leptospira is especially complex<sup>4</sup> and it is an advancing global health problem<sup>1</sup>. Rodents are the dominant and broadly distributed reservoirs of leptospira<sup>1</sup>. Among worldwide they were above 5000,000 sever cases in humans<sup>1</sup>, the world health organization's (WHO) epidemiology family evaluated that there were 1.03 million cases of leptospirosis with 58,900 death worldwide yearly, resulting that roughly about 2.9 million disability adjusted life years (DALs) lost each year<sup>9</sup>.

### Pathology:-

Leptospirosis acquires a linear framework of transmission adhesion and cell entry into host cells. It is an acute bacterial septicemia febrile illness caused by a pathogenic leptospira, which affect both human and animals; martins-pinheero conducted a silico research for DNA repair pathways in pathogenic leptospira. This allows them to identify a several important genes that are required for leptospiral infection the accurate molecular

pathophysiology relevant to leptospirosis bewildering quandary for many even though notifiable research have been made recently<sup>13</sup>.

Transmission occurs through infected animals, water or soil contaminated with urine from infected animals. The pathogenic leptospires enter into the body by penetrating mucous membranes or skin abrasions and disperse through the hematogenic route. In humans leptospirosis may cause a wide variety of symptoms mostly immune manifestations. The rigorous forms of disease may be mortal with multi organ damage together with renal failure, hepatic dysfunction, muscle lesions, pulmonary hemorrhage and vascular damage<sup>13</sup>.



**Fig-3:-** Pathogenesis of leptospirosis<sup>17</sup>

In this review we deliberate about the pathogenesis of leptospirosis. Pathogenic leptospires are extensive in nature potential gateways to leptospirosis are usually mucous membrane of oral cavity, skin abrasions and conjunctiva occupational activities involving infected animals water and contaminated soil are major risk factors for developing leptospirosis humans are unintentional hosts, for short durations they commonly exhibit urinary shedding of leptospirosis, however we should recollect that proximal tubules are the main site of important lesions during human and animal infections, leptospirosis can also be contemplate as a hemorrhagic septicemia as they involve vessels, mainly those of the microcirculatory circulation. Accordingly, VE-cadherin is a important identified receptor for pathogenic leptospirosis the binding of bacteria of VE-cadherin is arbitrated by adhesions lipoproteins and proteins Mastinez-lopez et al. demonstrated that pathogenic strains of leptospira did not cause necrosis of the cells even after the prolonged incubation period substantially disrupted the endothelial layers of cells which may be elucidated as main contributor to the hemorrhagic manifestations of disease<sup>13</sup>.

As we well known that the most severe form of leptospirosis is the Weil's disease mainly characterized by hemorrhage, hepatic and renal manifestations. Jaundice is an important clinical presentation of hepatic dysfunction but its mechanism is not completely elucidated. The jaundice is mainly due to elevated levels of conjugated bilirubin and disruption of bile excretion with intra hepatic cholestasis<sup>13</sup>.

Kidney is also a major target organ in leptospirosis and tubule- interstitial nephritis is the most familiar clinical and pathological manifestation clinically hypokalemia sodium and magnesium wasting frequently occurs in human leptospirosis<sup>13</sup>.

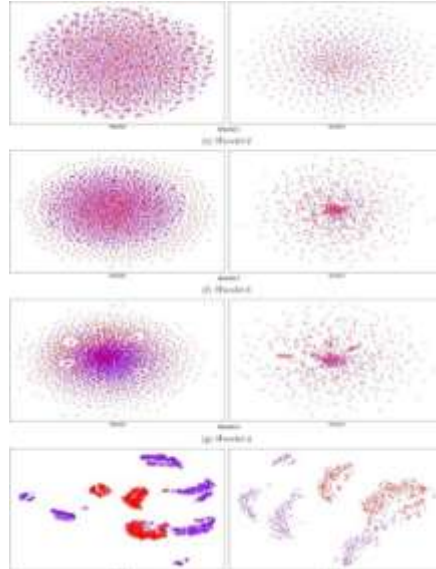
The most common lesion in leptospirosis is the vascular damage which affects the endothelial cells. In the leptospirosis vascular injury is present that is characterized by segmental lesions on the walls of coronary artery and their branches<sup>13</sup>. In brief leptospirosis seems to be the cell membrane damage mediated by some unknown factors, likely toxic cellular components or leptospiral proteins. Injuries to the cell membrane leading to significant organ dysfunction; Understanding the pathology of leptospirosis is of utmost importance for prognostic and therapeutic applications<sup>3</sup>.

### Diagnosis:-

Diagnosis is often made when clinical manifestations delineate Weil's disease, pulmonary hemorrhage, renal failure or jaundice is evident<sup>6</sup>. Leptospirosis is mostly diagnosed by detecting antibodies in blood<sup>7</sup>. The diagnostic tools which are most effective and accurate have been developed in order to affirm the occurrence of leptospirosis

infection. The currently accepted diagnostic tests for leptospirosis include serological tests like microscopic agglutination test (MAT it is the gold standard for sero-diagnosis of leptospirosis), solid phase as36say, enzyme linked immune-sorbent assay (ELISA) and indirect haemagglutination assay are the diagnostic methods<sup>6</sup>. The serological reference test was first represented in 1918 by martin and Pettit<sup>1</sup>.

Researchers and scientist also expanding other advanced techniques namely cytometry<sup>6</sup>, complement fixation, counter immune electrophoresis, indirect fluorescent antibody, sensitized erythrocytelysis, latex agglutination (LA), microscopic agglutination, patoc slide agglutination and microscopic slide agglutination<sup>1</sup>. The samples for culture should be cultured earlier to the administration of antibodies blood, dialysate and the cerebrospinal fluid these samples should be cultured in the first 10 days of illness. The samples that are collected should be stored and transfer at ambient at 28e30C and should be examined weekly by dark field microscopy up to 13 weeks earlier to be discarded. All these several specific media was expressed by Fletcher ET al<sup>1</sup>.



**Fig-4:-** Microscopic agglutination test<sup>19</sup>

On the basis of immunological theories rapid screening tests are applied<sup>1</sup>. Particle agglutination (in this whole blood is required for centrifugation) and detection of weak agglutination is difficult so it often requires refrigeration<sup>1</sup>.

Rapid screening tests are primarily IgM detection assays but IgM is not identifiable until the second week after the onset of symptom. When the patient presents for the treatment they have low sensitivity in the early acute phase of disease. In the Hawaii eight rapid tests have been assessed but the authors concluded that all the tests are inconsiderate for diagnosis within the initial period of disease<sup>1</sup>.

### **Treatment:-**

Initial treatment depends on the extremity of the disease<sup>3</sup>. Mild cases may not need antibiotics and sever cases may need supportive care in the intensive care unit as well as antibiotics<sup>7</sup>. In case of mild disease we esteem treatment with Doxycycline and Azithromycin and for pregnant women we esteem treatment with Azithromycin and Amoxicillin (table1). Adults who hospitalized for sever disease we esteem treatment with penicillin, Doxycycline and cephalosporin antibiotics like Ceftriaxone and Cefotaxime and in case of children who hospitalized for sever leptospirosis we esteem treatment with penicillin, Doxycycline, Ceftriaxone, Cefotaxime and Azithromycin( it is an alternative agent) (table2).Using of tetracycline's repeatedly in children less than 8 years (<8 yrs) may cause permanent tooth discoloration and Doxycycline can be used for  $\leq 21$  days in children in all ages because it binds less readily to calcium than other tetracycline's. Pregnant women with severe leptospirosis can be esteem with penicillin, Ceftriaxone, Cefotaxime or Azithromycin (since murine typhus does not respond as well as to Azithomycin as to Doxycycline)<sup>15</sup>.

<b>In mild cases</b>		
<b>Doxycycline</b>	In children	2mg/kg per day in two equally divided doses for 7 days ( not exceed 200mg daily)
	In adults	100mg orally twice daily for seven days
<b>Azithromycin</b>	In children	10 mg/kg orally on day 1 (maximum 500mg/day) followed by 5 mg/kg/day orally once daily on subsequent days (maximum 250mg/day)
	In adults	500mg orally once daily for seven days
<b>Azithromycin</b>		500mg orally once daily for three days
<b>Amoxicillin</b>	In pregnant women	25-50 mg/kg in three equally divided doses for seven days (maximum 500mg/dose)

Table-1

<b>In severe cases</b>		
<b>Doxycycline</b>	In adults	100mg IV twice daily
<b>Ceftriaxone</b>		1-2g IV once daily
<b>Cefotaxime</b>		1g IV every six hours

<b>Doxycycline</b>		4mg/kg/day IV in two equally divided doses(maximum dose-200mg/day)
<b>Ceftriaxone</b>		80-100mg/kg IV once daily(maximum dose 2g daily)
<b>Cefotaxime</b>	In children	100-150mg/kg/day IV in 3-4 equally divided doses
<b>Azithromycin</b>		10mg/kg IV on day 1(maximum dose 500mg/day), followed by 500mg/kg/day IV once daily on subsequent days (maximum dose 250mg/day)

Table – 2

Antibiotic treatment has been shown to minimize symptoms include malaise, headache and fever by toe days, and to stop leptospirosis. Children and pregnant women should avoid taking doxycycline. Azithromycin and doxycycline is the drug of choice in areas where rickettsial diseases are widely distributed. A Jarisch-Herxheimer reaction can flourish, usually within the first few hours after antibiotic administration. Penicillin G sodium IV is recommended treatment for severe cases, where penicillin G demonstrated some notable reductions in hospital duration, creatinine elevation and fever duration<sup>3</sup>. Desmopressin has also been evaluated as ancillary treatment. Use of corticosteroids IV and plasmapheresis has been suggested given the vasculitic nature for severe leptospirosis; but there is inadequate evidence for routine use of both corticosteroids and plasmapheresis<sup>15</sup>.

### Prevention:-

Soil or water which is contaminated with animal urine should be avoided.  
 When swimming in rivers or lakes avoid swallowing of water.  
 Cover the cuts and scrapes heal with bandages before submerging in possibly contaminated water.  
 Minimize rodent populations whenever feasible. (7).

### Conclusion:-

Leptospirosis is apparently the most frequent, underestimated and re-emerging zoonosis disease. Carrying may occur more routinely on shores where people are likely to be shoeless. Patients with leptospirosis may experience some risk factors like hepatic and renal dysfunctions with neutrophilia and anemia, thrombocytosis and leucocytosis were the hematological changes. Patient with leptospirosis may choose antibiotics based on the cost, conviction of diagnosis, convenience and clinical support.

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