Leptospirosis is the most common zoonosis of worldwide distribution. It is an emerging infectious disease of global importance, as illustrated by recent large outbreaks in Asia, Central and South America, and the United States.

SYNONYM
Swineherd’s disease, swamp fever, or mud fever.

ETIOLOGIC AGENTS
It is a Spirochetal disease caused by leptospire. The genus *Leptospira* comprised two species:
2. Non pathogenic leptospires - *L. Biflexa*.

These are coiled thin highly motile organisms with hooked ends and two periplasmic flagella that permit burrowing into tissues (Fig.1).

Specific serotype associated with different hosts:
- Pomona - Livestock
- Canicola - Dogs
- Icterohemorrhagiae - Rodents

The pathogenic leptospires are divided into serovars according to their antigenic composition. More than 250 serovars make up the 26 serogroups.

EPIDEMIOLOGY
Leptospirosis is an important zoonosis with a worldwide distribution. It appears to be ubiquitous in wildlife & in many domestic animals. Most important reservoir is rodents (especially rats); others are swine, dogs, cats, raccoons, cattle.

This infection more commonly affects males than females and occurs in the tropics more frequently than in western countries because the climate as well as the poor hygienic conditions in tropics favours the pathogen’s survival and distribution.

The leptospires are often transmitted to humans by the ingestion of food and drink contaminated by the urine of the reservoir animal. The organism may also enter through minor skin lesions and probably via the conjunctiva (milkers may be splattered in the face).

These microorganisms establish a symbiotic relationship with their animal host and can persist in the renal tubules for months to years and are shed into the urine in massive numbers with affecting their host. Leptospirosis in humans
after infection is more transient, rarely lasting more than 60 days. With rare exceptions, man represents a dead end in the chain of infection because person-to-person spread of the disease is rare.

Although national incidence data is not available for India, published data is available for Andaman islands, one of the most endemic areas of the world with a documented incidence rate of 50/100,000. In 1999, more than 500,000 cases were reported from China, with case-fatality rates ranging from 0.9 to 7.9%. Mortality in icteric leptospirosis is 5-40%. A significant rise in the incidence has occurred in North India in recent years.

Since leptospires are excreted in the urine and can survive in water for many months, water is an important vehicle in their transmission. Epidemics of leptospirosis may result from exposure to flood waters contaminated by urine from infected animals, as has been reported from Nicaragua.

**EPIDEMIOLOGICAL FORMS**

**Occupational** is the main way of contracting leptospirosis in temperate climates. Certain occupational groups are at especially high risk; included are veterinarians, agricultural workers, sewage workers, slaughterhouse employees, and workers in the fishing industry - either through direct exposure or contact with contaminated water & soil.

**Rural Leptospirosis** is the consequence of a wider environmental contamination in particular during the wet season when outbreaks can occur configuring an epidemic-endemic pattern of disease.

**Urban Leptospirosis** is often seen in overcrowded cities and towns where environmental sanitation and personal hygiene are poor.

**Rercreational Leptospirosis** exemplified by the outbreak among participants of the multi-sport racing expedition in Malaysia. Several large point-source water-borne outbreaks have occurred recently following athletic events.

**Leptospirosis associated with natural disasters** as exemplified by post disaster outbreaks following Orissa cyclone (Oct. 1999, Paradip) and the Mumbai flash flood (July 2005).

**PATHOGENESIS**

The organism gains entry in the body through skin abrasions, or intact mucosa like conjunctiva, oro & naso-pharynx, gut epithelia (after ingestion of contaminated water). After entry into the host it multiplies in the blood and tissues including CSF causing pleocytosis but clinical meningitis only in minority. All forms of leptospires can damage the wall of small blood vessels causing vasculitis with leakage and extravasation of cells, including haemorrhages. Vasculitis is responsible for the most important manifestations of the disease. The most important known pathogenic properties of leptospires are adhesion to cell surfaces and cellular toxicity. Although leptospires mainly infect the kidneys and liver, any organ may be affected.

**Kidney** - Leptospires migrate to the interstitium, renal tubules, and tubular lumen, causing interstitial nephritis and tubular necrosis. Much recent work has focused on the role of surface lipoprotein. The major surface lipoprotein, LipL32, is highly conserved among pathogenic serovars. LipL32 is a major target of the human immune response and appears to be involved in pathogenesis of tubulointerstitial nephritis.

**Liver** - Centrilobular necrosis with proliferation of Kupffer cells may be found. However, severe hepatocellular necrosis is not a feature of leptospirosis.

**Pulmonary** - Involvement is the result of hemorrhage and not of inflammation.

**Skeletal muscle** - Invasion by leptospires results in swelling, vacuolation of the myofibrils, and focal necrosis.

In severe leptospirosis, vasculitis may ultimately impair the microcirculation and increase capillary permeability, resulting in fluid leakage and hypovolemia. When antibodies are formed, leptospires are eliminated from all sites in the host except the eye, the proximal renal tubules, and perhaps the brain, where they may persist for weeks or months. The persistence of leptospires in the aqueous humor occasionally causes chronic or recurrent uveitis.

**CLINICAL MANIFESTATIONS:**

Incubation period - 1-2 wks (2-20 days).

Many Leptospira-infected persons remain asymptomatic & more than 90% of symptomatic persons have relatively mild and usually anicteric form of leptospirosis, with or without meningitis. Severe leptospirosis with profound jaundice
(Weil’s syndrome) develops in only 5-10% of infected individuals.2 The idea that distinct clinical syndromes are associated with specific serogroups has been refuted, although some serovars tend to cause more severe disease than others. The natural course of leptospirosis falls into two distinct phases:

1. First phase or Septicaemic/leptospiremic phase
2. Second phase or Immune/leptospiruric phase

The distinction between the first and second phases is not always clear, and milder cases do not always include the second phase.

First phage (Septicemic or leptospiremic)

- This stage is called the septicemic or leptospiremic stage because the organism may be isolated from blood cultures, cerebrospinal fluid (CSF), and most tissues.
- During this stage, which lasts about 4-7 days, the patient develops a nonspecific flulike illness of varying severity.
- It is characterized by fever, chills, weakness, and myalgias, primarily affecting the calves, back, and abdomen.
- Other symptoms include sore throat, cough, chest pain, hemoptysis, rash, frontal headache, photophobia, mental confusion, and other symptoms of meningitis.
- Because of the abrupt nature of the onset, the patient can often tell exactly when the symptoms started.

For a brief period of 1-3 days between 2 phases of leptospirosis patients show some improvement and become relatively asymptomatic. The fever then recurs, indicating the onset of the second phase when clinical or subclinical meningitis appears.

Second phage (Immune or leptospiruric phase)

- This stage is called the immune or leptospiruric stage because circulating antibodies may be detected or the organism may be isolated from urine; it may not be recoverable from blood or CSF.
- This stage occurs as a consequence of the body’s immunologic response to infection and lasts 0-30 days or more.
- Nonspecific symptoms, such as fever and myalgia, may be less severe than in the first stage and last a few days to a few weeks.
- Disease manifestation referable to specific structure/ organs is seen and these are usually meninges, liver, kidneys, and eyes related.

Meninges - Many patients (77%) experience headache that is intense and poorly controlled by analgesics; this often heralds the onset of meningitis. Aseptic meningitis is the most important clinical syndrome observed in the immune anicteric stage. Symptoms may be nonspecific, and a viral etiology may be suspected. Meningitis usually lasts a few days but occasionally lasts 1-2 weeks. Death is extremely rare in the anicteric cases.

Liver - Leptospires may be isolated from the blood for 24-48 hours after jaundice appears. Abdominal pain with diarrhea or constipation (30%), hepatosplenomegaly, nausea, vomiting, and anorexia are also seen.

Kidneys - Renal symptoms (eg pyuria, hematuria, oliguria) are seen in 50% of patients with leptospirosis. Leptospires may be present in the kidney and may be isolated from urine. Eyes - Subconjunctival hemorrhage (92%) is the most common ocular complication of leptospirosis. Leptospires may be present in the aqueous humor. Uveitis (2-10%), iridocyclitis and chorioretinitis can develop early or late in the disease and has been reported to occur as late as one year after initial illness.

Pulmonary manifestations

Occur in 20-70% of patients, usually have a benign course, and may occur in both the icteric and anicteric forms of the disease. Pulmonary involvement usually as a result of

- Pulmonary hemorrhage or
- Acute respiratory distress syndrome

Indeed, the severe pulmonary form of leptospirosis (SPFL) is considered to be one of the major causes of death in patients with severe leptospirosis. Lymphadenopathy, rashes, and muscular pain are also seen.

Weil’s syndrome needs special mention. It is the most severe form of leptospirosis and primarily manifests as profound jaundice, renal dysfunction, hepatic necrosis, pulmonary dysfunction, and hemorrhagic diathesis.

- It occurs at the end of the first stage and peaks in the second stage; however, the patient’s condition can deteriorate suddenly at any time. Often, the transition between the stages is obscured.
- Fever may be marked during the second stage.
- Criteria to determine the development of Weil’s disease are not well defined.
- Pulmonary manifestations include cough, dyspnea, chest pain, hemoptysis, and respiratory failure.
- Vascular and renal dysfunction accompanied by jaundice develops 4-9 days after onset of disease, and jaundice
Patients with severe jaundice are more likely to develop renal failure, hemorrhage, and cardiovascular collapse. Hepatomegaly and tenderness in the right upper quadrant may be present. Oliguric or anuric acute tubular necrosis may occur during the second week due to hypovolemia (fluid leakage due to increased capillary permeability) and decreased renal perfusion. Multiorgan failure, rhabdomyolysis, adult respiratory distress syndrome, hemolysis, splenomegaly, congestive heart failure, myocarditis, and pericarditis may also occur. Weil’s syndrome carries a mortality rate of 5-15%. The most severe cases with hepatorenal involvement and jaundice, have a case-fatality rate of 20-40%. The mortality rate is usually higher for older patients.

LABORATORY AND RADIOLOGICAL FINDINGS

Routine blood
The erythrocyte sedimentation rate is usually elevated. In anicteric leptospirosis peripheral leukocyte counts range from 3000 to 26,000/cmm, with a left shift; in Weil’s syndrome, leukocytosis is often as high as 50,000/cmm with neutrophilic predominance. Mild thrombocytopenia occurs in up to 50% of patients and is associated with renal failure.

Urine
Urinary sediment changes (leukocytes, erythrocytes, and hyaline or granular casts) and mild proteinuria are seen in anicteric leptospirosis to renal failure. Urine culture may be positive from 10 days to 6 weeks.

Blood biochemistry
Elevated serum levels of bilirubin and alkaline phosphatase (ALP) as well as mild increases in serum levels of aminotransferases (up to 200 U/L). In Weil’s syndrome, the prothrombin (p-time) time may be prolonged but can be corrected with vitamin K.

Levels of creatine phosphokinase (CK), which are elevated in up to 50% of patients with leptospirosis during the first week of illness, may help to differentiate this infection from viral hepatitis.

Varying degrees of azotemia is seen. Creatinine > 1.5mg/dl is seen in more than one-half of the patients.

CSF
When a meningeal reaction develops, polymorphonuclear leukocytes predominate initially and the number of mononuclear cells increases later. The protein concentration in the CSF may be elevated; CSF glucose levels are normal.

Radiology
The most common radiographic finding in X-ray chest is a patchy alveolar pattern that corresponds to scattered alveolar hemorrhage. Radiographic abnormalities most often affect the lower lobes in the periphery of the lung fields.

Confirmation of Diagnosis
High clinical suspicion is necessary in appropriate setting. To confirm the diagnosis the following may be done.

Isolation of the organism
Leptospires are readily cultured in polysorbate-albumin media - special media named EMJH/Fletcher/Korthof media. Blood or urine sample is used for culture but this needs several weeks. So time factor is limiting its utility in clinical practice.

Serology
Agglutination tests (microscopic, using live organisms, and macroscopic, using killed antigen) become positive after 7-10 days of illness, peak at 3-4 weeks, and may persist at high levels for many years. The most commonly used technique is Microscopic agglutination test (MAT). To make a diagnosis, a fourfold or greater rise in titer between acute- and convalescent-phase serum specimens must be documented. In cases with strong clinical evidence of leptospire infection, a single antibody titre of 1:200-1:800 (depending on whether the case occurs in a low- or high-endemic area) in the MAT is required. The agglutination tests are cumbersome to perform and require trained personnel.

Indirect hemagglutination and enzyme-linked immunosorbent assay (ELISA) tests are also available and they may be useful in the first 3-5 days of infection.

The IgM EIA is particularly useful in making an early diagnosis, since it is positive as early as 2 days into illness, a time when the clinical manifestations may be nonspecific, and it is extremely sensitive and specific (93%).

The antibody response can be affected by early treatment. Antibodies generally do not reach detectable levels until the second week of illness. Recently developed
immunochromatographic technique shows reasonable sensitivity.

**Polymerase chain reaction** techniques have been developed but so far have not found wide spread use outside research and reference laboratories. **Dark field examination**, though cheap and rapid form of diagnosis, it is not recommended because of frequent misdiagnosis.

**DIFFERENTIAL DIAGNOSIS**
Leptospirosis should be differentiated from other febrile illnesses associated with headache and muscle pain, such as dengue, malaria, enteric fever, viral hepatitis, *Hantavirus* infections, and rickettsial diseases.

In light of the strong similarity in epidemiology and clinical presentation between leptospirosis and *Hantavirus* infections and given the reported occurrence of dual infections, it is advisable to conduct serologic testing for *Hantavirus* in cases of suspected leptospirosis.

**TREATMENT**
The Cochrane Database of Systematic Reviews concluded that evidence from randomized clinical trials is insufficient to provide clear guidelines for the treatment of leptospirosis.15 Contrary to previous belief ceftriaxone and cefotaxime are equally effective to penicillin. Doxycycline and azithromycin are also effective alternatives2. Treatment should be given as quickly as possible but therapy given after first four days of illness is still effective. (Table I)

It is worth mentioning that even appropriate antibiotic treatment may not prevent development of renal failure. Renal failure is fully reversible though patient may require temporary support with peritoneal or hemodialysis.

Patients of Weil’s syndrome may require additional therapy in the form of blood transfusion, platelet transfusion, FFP. They may need ICU care for ventilatory support and critical monitoring.

**Note: Jarisch-Herxheimer reaction**
Within hours after the initiation of antimicrobial therapy patient may rarely develop Jarisch-Herxheimer reaction. So far the only effective mode of management is supportive; the role of antibodies to tumor necrosis factor in the treatment of this reaction deserves further study.

**PROGNOSIS**
Most patients with leptospirosis recover. Mortality rates are highest among patients who are elderly and those who have Weil’s syndrome. Leptospirosis during pregnancy is associated with high rates of fetal mortality. Long-term follow-up of patients with renal failure and hepatic dysfunction has documented good recovery of renal and hepatic function.

**PREVENTION**
The following points are to be stressed upon...
1. Education of at risk population is required.
2. Vaccination of the reservoir animals.
3. Avoidance of exposure to urine and tissues of infected animals.
4. Rodent control program.
5. Vaccination of human beings tried but without much success.
6. Chemoprophylaxis with doxycycline has appeared to be efficacious to some extent but is indicated only in rare instances of sustained short-term exposure.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Compound</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Chemoprophylaxis</td>
<td>Doxycycline</td>
<td>200mg once a week (oral)</td>
</tr>
<tr>
<td>Mild leptospirosis</td>
<td>Doxycycline</td>
<td>100mg twice daily (oral)</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>500-750mg 6 hrly (oral)</td>
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<tr>
<td></td>
<td>Amoxicillin</td>
<td>500mg 6 hrly (oral)</td>
</tr>
<tr>
<td>Mod. to severe</td>
<td>Penicillin G</td>
<td>1.5 MU IV 6 hrly</td>
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<tr>
<td>Leptospirosis</td>
<td>Ceftriaxone</td>
<td>1 g IV 24 hrly</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>0.5g IV 6 hrly</td>
</tr>
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All regimens used for treatment are administered for 7 days.
KEYNOTES

- When patients have a flu-like disease with disproportionately severe myalgia or aseptic meningitis, a diagnosis of leptospirosis should be considered.
- Rodents (especially rats) - most important reservoir.
- It is advisable to conduct serologic testing for Hantavirus in cases of suspected leptospirosis because of close similarity of epidemiology & clinical features of these two diseases.
- Penicillin ceftriaxone and cefotaxime are equally effective. Doxycycline and azithromycin are also effective alternatives.

REFERENCES