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Leptospirosis: Report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine☆

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ABSTRACT

Leptospirosis is a zoonosis caused by a gram negative aerobic spirochete of the genus *Leptospira*. It is acquired by contact with urine or reproductive fluids from infected animals, or by inoculation from contaminated water or soil. The disease has a global distribution, mainly in tropical and subtropical regions that have a humid, rainy climate and is also common in travelers returning from these regions. Clinical suspicion is critical for the diagnosis and it should be included in the differential diagnosis of any patient with a febrile hepatorenal syndrome in, or returning from endemic regions.

The leptospiremic phase occurs early and thereafter there is an immunologic phase in which the most severe form, Weil's disease, occurs. In the latter, multiple organ dysfunction predominates. The appropriate diagnostic test depends on the stage of the disease and consists of direct and indirect detection methods and cultures.

Severely ill patients need to be monitored in an ICU with appropriate anti-bacterial agents and early, aggressive and effective organ support. Antibiotic therapy consists of penicillins, macrolides or third generation cephalosporins.

Contents

☆ On behalf of the Council of the World Federation of Societies of Intensive and Critical Care Medicine.

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1. Introduction

Leptospirosis is a zoonosis caused by a gram negative aerobic spirochete of the genus *Leptospira* [1]. Overall 21 species potentially pathogenic to humans such as *Leptospira interrogans* have been catalogued by DNA mapping, however some such as *Leptospira biflexa are not*. The most severe presentation of leptospirosis was first described by Adolf Weil in Heidelberg, Germany in 1886, and it is therefore known as Weil's disease [1].

Leptospirosis is acquired by contact with urine or reproductive fluids from infected animals, mainly rodents, or by contaminated water or soil through abrasions, conjunctiva and mucous membranes with dissemination to the central nervous system, vitreous humor, lungs, heart, liver, and kidneys. As such certain lifestyles or occupations increase risk, for example, cattle ranchers, construction workers and adventure sportsmen are more likely to contract the disease.

2. Epidemiology

The disease has a global distribution, mainly in tropical and subtropical regions that have a humid, rainy climate. The number of infections are probably underestimated because of the wide variety of presentations including those that have only an influenza-like illness. Annually it is estimated that there are 1.03 million cases (95% CI 434,000–1,750,000) and 58,900 deaths (95% CI 23,800–95,900) due to leptospirosis worldwide. A large proportion of cases (48%, 95% CI 40–61%) and deaths (42%, 95% CI 34–53%) occur in adult males between the age of 20–49 years. The greatest morbidity and mortality have been observed in South and Southeast Asia, Oceania, Caribbean, Andean, Central, and Tropical Latin America, and East Sub-Saharan Africa [2] where deficiencies in the sanitation infrastructure and social factors produce unequal health outcomes and are important factors in *Leptospira* transmission [3]. The disease is also common in returning travelers. In the recent GeoSentinel Study recording the incidence of Tropical or Subtropical Diseases reported in western travelers in the years 1996–2011, 82,825 ill patients sought medical care, of which 3655 (4.4%) with 3666 diagnoses were acute, potentially life-threatening conditions. The most frequent of these were falciparum malaria (76.9%), typhoid (11.7%), paratyphoid (6.4%) and leptospirosis (2.4%) [4].

Of those admitted to hospital the overall mortality ranges from 4 to 52%. In the intensive care unit (ICU) the mortality is estimated to exceed 52%, much higher than the mortality of other patients in the medical ICU (31.4%) in the same period. The poor prognostic factors are: age (>40 years), multiple organ dysfunction syndrome (MODS), acute kidney injury (AKI), respiratory failure and cardiovascular compromise [5-9].

3. Clinical features

Clinical suspicion is critical for the diagnosis and it should be included in the differential diagnosis of any patient with a febrile hepatorenal syndrome in or returning from endemic regions.

3.1. Leptospiremic phase

This usually occurs within 5 to 7 days during which the organisms disseminate diffusely through the bloodstream. The illness generally presents with the abrupt onset of fever, rigors, myalgias, and headache in 75 to 100% of patients [10]. Conjunctival suffusion is a frequent manifestation and may be associated with sub-conjunctival hemorrhages. Nonproductive cough occurs in 20 to 57% and nausea, vomiting and diarrhea occur in approximately 50% [10,11]. Death is rare at this stage, and the symptoms may resolve.

3.2. Immunologic phase

Maximal organ injury occurs in this phase. It occurs between days 4 to 30 after the initial phase and if it occurs it is known as Weil's disease. Thereafter the patient may develop renal failure, jaundice, cardiac dysrhythmias, aseptic meningitis, conjunctival injection (with or without hemorrhage), ocular pain, myalgia, adenopathy, and hepatosplenomegaly. Muscle tenderness and rigidity, splenomegaly, lymphadenopathy, pharyngitis, hepatomegaly, abnormal respiratory auscultation, or skin rash occur in 7 to 40% of patients [12]. Less common symptoms include arthralgias, bone pain, sore throat, and abdominal pain. Acalculous cholecystitis and pancreatitis have been described in children and vasculitis with necrosis of the extremities may be seen in severe cases [13].

4. Pathogenesis of Weil disease

4.1. Renal failure

The primary manifestation consists of non-oliguric renal failure associated with hypokalemia and hyponatremia due to increased fluid loss. Leptospirosis has the capacity to act directly on electrolyte transport mechanisms, inducing derangements of sodium (Na^+), chloride (Cl^-) and potassium (k^+) by inhibiting the Na^+K^+Cl cotransporter. Urea nitrogen is usually below 100 mg/dL, and creatinine between 2 and 8 mg/dL. AKI develops as a consequence of dehydration, interstitial nephritis and possibly immune complex mediated glomerulonephritis. Urinalysis frequently shows proteinuria, pyuria, granular casts, and occasionally microscopic hematuria [14-19].

4.2. Hepatic

Liver histopathologic findings include degeneration of hepatocytes, Kupffer cell hypertrophy, erythrophagocytosis, cholestasis, mononuclear infiltrates, but with an absence of necrotic foci. The bilirubin levels can rise as high as 80 mg/dL but more frequently remain in the region of 30–40 mg/dL, with transaminase levels below 200 U/L in approximately 40% of patients [20,21].

4.3. Hematologic features

Leptospirosis presents with a peripheral leukocytosis generally less than 10,000/μL but may range from 3000 to 26,000/μL with a left shift. Thrombocytopenia is frequent even in the absence of disseminated

intravascular coagulation (DIC) and pancytopenia has been reported [8,22].

4.4. Cardiovascular

Histologic findings are those of an interstitial myocarditis with involvement of the conduction system, as well as coronary arteritis and aortitis [17]. This manifests as cardiac failure and arrythmias [23].

4.5. Pulmonary hemorrhage syndrome

Although this usually occurs in association with Weil's disease it may be the only manifestation. Dyspnea or coughing occur early, sometimes associated with hemoptysis. The radiologic findings of bilateral lower lobe infiltrates are caused by diffuse alveolar hemorrhage [24-27].

Meningoencephalitis and/or aseptic meningitis is manifested by meningismus and delirium [28,29]. In a series with neuro-leptospirosis, the CT scan was normal in 18 of 27 (67%), while 7 (26%) had diffuse cerebral oedema. Cerebrospinal fluid CSF pleocytosis with lymphocytic predominance (mean 50 cells/microl) and elevated protein levels (mean 115.5 ± 67.5 mg %) were noted. *Leptospira* antibody was detected in serum of all, and in 5 of 22 in CSF samples [30]. Other neurologic manifestations such as transverse myelitis, hemiplegia and Guillain-Barré syndrome are infrequent [11].

5. Differential diagnosis

Leptospirosis may be difficult to distinguish from many other infectious illnesses The differential includes dengue, chikungunya, influenza, hantavirus and other acute viral illnesses; bacterial illnesses such as *Salmonella typhi*, meningococcemia, and ehrlichiosis, rickettsial diseases such as Scrub typhus, Rickettsia typhi and protozoal (malaria) [28,31]. Conjunctival suffusion, when it occurs, is one of the most reliable distinguishing features since it rarely occurs with any infectious illness other than the viral haemorrhagic fevers.

6. Laboratory diagnosis

The value of the various diagnostic tests depends on the stage of the disease and whether the patient has received antibiotics [32,33].

6.1. Direct detection methods

In the leptospiremic phase, the organism can be seen in the in urine and blood using a darkfield microscope, though the method is not very sensitive (40.2%) or specific (61.2%) [34]. The most sensitive method is the reverse transcriptase-polymerase chain reaction (RT-PCR).

6.2. Cultures

The sample (CSF, blood, and peritoneal fluid) must be obtained during the febrile phase in the first 10 days of the illness, and prior to antibiotic administration. The sample should be placed in the culture medium immediately, preferably at the bedside and processed within an hour as the viability of the organism is limited. Isolation of the organism is successful in from 5 to 50% of cases but may take several weeks [31,35]. Urine cultures remain positive for up to 30 days after the resolution of symptoms.

6.3. Indirect methods

The microscopic agglutination test (MAT) performed on the patient's serum is considered the reference standard for development of other assays and the detection of *Leptospira* IgM. Results are considered positive when titers increase fourfold or greater between the acute and convalescent specimens, however a single titer of >1:800 is reasonable evidence of current or recent infection. Its greatest limitation is poor sensitivity in the initial phases but may be positive after day 5 of symptom onset. Although the MAT is highly specific, the time required between testing of acute and convalescent sera and the requirement of a 4-fold increase in titer renders the test most useful for retrospective confirmation of the disease [33].

7. Management

Leptospirosis is a disease with definitive and specific therapy with an excellent possibility of recovery, even in the severely ill population. Patients presenting with severe leptospirosis need to be closely monitored in an ICU and provided with appropriate anti-bacterial agents and early, aggressive and effective organ support. When treated early complete recovery is possible.

7.1. Admission to the ICU

Patients do not require special isolation measures; however, level 2 biosafety measures must be maintained, especially with regard to exposure to body fluids such as blood and urine [31].

The following clinical findings confer a higher risk of death [5,11,36]; age >30 years, AKI, respiratory failure, hypotension, arrhythmias, altered mental status and severe jaundice (Bilirubin > 15 mg/dL).

Therapy is essentially supportive and consists of aggressive fluid and electrolyte replacement, however avoiding fluid overload is critical. Hemodynamic support may be necessary and vasopressor use should follow the Surviving Sepsis Campaign guidelines [37,38]. Arrhythmias should be managed appropriately. No specific therapy is required for hepatic dysfunction, but renal replacement therapy in the presence of AKI, has been shown to be effective [18,19,36,39]. Mechanical ventilation should be employed as required, however despite this, the mortality of the severe pulmonary hemorrhage syndrome is >50% and it is possible that extracorporeal membrane support might be of value in this setting [24].

7.2. Pregnancy

Leptospira infection can result in miscarriage in >50% of patients in some series. Late infections can result in vertical transmission of active leptospirosis at birth but this does not appear to be associated with congenital abnormalities or long-term sequelae in those children that survive; as such, leptospirosis acquired in pregnancy is not an indication for termination [13,31].

8. Treatment

Antibiotics should be administered as soon as possible (Table 1). However, most patients present in advanced stages of the disease and

Table 1
Leptospirosis treatment: selection by disease indication.

Indication	Antibiotic	Dosage
Mild leptospirosis	Doxycycline	100 mg orally twice daily for 5–7 days, or 100 mg IV daily for 7 days
	Ampicillin	500–750 mg orally every 6 h, or 0.5–1 g IV every 6 h
	Amoxicillin	500 mg orally every 6 h
	Azithromycin	1 g orally, then 500 mg daily for 2 days
Moderate to severe leptospirosis	Penicillin G	1.5 million units IV every 6 h
	Ampicillin	500–750 mg orally every 6 h, or 0.5–1 g IV every 6 h
	Ceftriaxone	1–2 g IV daily for 7 days
	Doxycycline	100 mg orally, twice daily for 5–7 days or 100 mg IV daily for 7 days
Prophylaxis	Doxycycline	200 mg orally per week

Abbreviation: IV, intravenous.

often have multiorgan compromise, making the impact of antibiotic therapy more difficult to determine [40-44]. A Jarisch-Herxheimer reaction, (rigors, fever, and potentially severe hypotension) can occur within 2 h of administration of penicillin or tetracycline in up to 21% of patients [45,46].

Plasmapheresis has been tried in severe leptospirosis with anecdotal benefit in patients with severe hepatic and renal dysfunction and in some cases of pulmonary alveolar hemorrhage but has never been proved for regular use [47-49]. Over the years corticosteroids have been used with mixed results.

Four studies demonstrated a potential benefit in severe leptospirosis with pulmonary involvement when administered early in the course of the illness, but these studies had several methodological flaws [50]. Desmopressin as an adjunct has been attempted with no clear benefit [51,52].

9. Prevention

Disease prevention should be based on avoiding contact with the bacteria while in high-risk environments. A vaccine is useful, but may not be readily available in some countries. Doxycycline, 200 mg weekly, as chemoprophylaxis has been recommended, however when this should be taken and who should take it is uncertain [31,53].

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