Human Leptospirosis: Management and Prognosis

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ABSTRACT
As leptospirosis is a treatable disease, early diagnosis and prompt treatment are important for better prognosis. Early diagnosis depends on the knowledge of epidemiological factors, presenting features and use of appropriate laboratory tests. Early institution of appropriate antimicrobial therapy in combination with supportive therapy reduces the mortality from this disease. Leptospires are sensitive to a variety of antimicrobial agents, including penicillin, cephalosporins, aminoglycosides, tetracyclines and macrolides. Of these antimicrobial agents, short-term treatment with streptomycin exterminates leptospires. When penicillin, cephalosporins, tetracyclines and macrolides are used, long-term therapy with large doses may be required from the early stage of the disease until the appearance of antibodies.

KEY WORDS: Antimicrobial agent, Chemotherapy, Leptospirosis, Management, Prognosis, Weil's disease

Human leptospirosis, an acute febrile illness that presents with a wide variety of clinical manifestations, is encountered throughout the world, especially in tropical and subtropical areas with high rainfall. The epidemics tend to follow natural disasters such as cyclones and floods. Leptospirosis is a treatable disease, and hence early diagnosis and prompt treatment are important for the improvement of prognosis. Although, efforts to reach a definitive diagnosis should always be undertaken, prompt institution of pertinent therapy should take precedence, as patients with leptospirosis are known to demonstrate a rapid deterioration in their clinical course. This is especially so as the serological tests do not yield a positive result for about a week after the onset of illness, and cultures may not become positive for several weeks. Under such circumstances, therapy could be initiated on the basis of clinical manifestations under appropriate epidemiological situations.

Collecting evidence for diagnosing leptospirosis

In the medical examination, medical professionals must always keep leptospirosis in mind to allow for early suitable treatment. The clinical manifestations of leptospirosis are variable, ranging from mild febrile illness to icteric-haemorrhagic illness with dysfunction of several organ-systems. The diagnosis is suspected on the basis of a combination of evidences generated by clinical manifestations, laboratory findings, clinical course and above all, epidemiological features (location, season, habits, occupation, contact with animals, travel to endemic areas, leisure activities, etc.). The most characteristic clinical signs for early diagnosis are acute febrile illness of sudden onset, severe general malaise, lumbago, muscular pains and conjunctival suffusion. Proteinuria, raised erythrocyte sedimentation rate, and leucocytosis with neutrophilia are the most indicative clinical laboratory findings for early diagnosis.

Serum aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT) and lactic dehydrogenase (LDH) levels are slightly elevated even in severe patients with jaundice. These findings are very important in differentiating between leptospirosis and viral hepatitis. Although, jaundice and haemorrhage are the most important signs of the severe form of leptospirosis, they are rarely useful in early diagnosis.

Management

Appropriate chemotherapy and supportive therapy help reduce the mortality of severe cases. Early treatment is very important. If the disease is not treated appropriately within the first 2–3 days, it may progress in severity. In the olden days, immune horse serum or specific immunoglobulin were used, and proved to be effective when given early. However, availability of effective antimicrobial therapy has supplanted the use of these remedies. Effective antimicrobial therapy should also be initiated before the fifth day after the onset of illness.

General management and supportive therapy
General management of leptospirosis includes providing symptomatic and supportive therapy, as indicated by the nature and severity of the symptoms and signs. Bed rest is required for 1–2 weeks in the mild forms, and for 2–4 weeks in the severe forms. Return to work should be gradual. The progress is monitored with routine measurement of temperature, pulse rate and blood pressure, monitoring of the urinary output and fluid balance, and review of tests such as complete blood count, erythrocyte sedimentation rate, liver function tests, urinalysis, blood urea nitrogen (BUN), creatinine and electrolyte analysis.

Chest radiograph, electrocardiogram, determination of bleeding, clotting and prothrombin time, and analysis of cerebro-
pinal fluid are also important and are done to determine the severity of illness and for detection of complications.

Restriction of fluid intake and provision of a high carbonate, low protein diet are desirable in subjects with renal involvement. Headache and muscular pains are treated with analgesic agents, and fever is managed with antipyretic agents. Intravenous injection of diazepam is very effective in controlling convulsions. Role of appropriate fluid management strategy titrated to clinical manifestations, state of illness and presence or otherwise of renal involvement cannot be over-emphasized. Oliguria due to dehydration or hypotension should be corrected and urine output maintained through fluid supplementation and restitution of blood pressure. After hydration and correction of blood pressure, furosemide (with doses up to 1000 mg/day) may be used to ensure adequate diuresis. Severe and worsening renal failure is treated with dialysis. It is advisable to institute dialysis early, as soon as BUN level reaches 200 mg/dl. Peritoneal dialysis is preferred to haemodialysis, as it is technically simpler. Plasmapheresis with dialysis may be effective for serious case with disturbance of consciousness. [27]

Myocarditis requires pertinent cardiological treatment. Management of bleeding and thrombocytopenia may require packed cell transfusion, or platelet transfusion, respectively. Some authorities believe in prudent use of steroids in subjects with severe manifestations. However, association of remarkable haemorrhage, and macroscopic and histological changes with steroid therapy in experimentally infected guinea pigs cast doubts over its use. [28]

**Chemotherapy**

Leptospires are sensitive to a variety of antimicrobial agents, including penicillin, cephalosporins, tetracyclines and macrolides. [29–47] Of these antimicrobial agents, penicillin and cephalosporins have the lowest minimal inhibitory concentrations (MIC) against leptospires in vitro. [29,29,41] The results of several studies have shown that penicillin kills leptospires in the logarithmic growth phase, but not in the stationary phase. [29,36,41] The same is true of cephaloridine, cefazolin and erythromycin. [37,41,44] Streptomycin has been shown to kill leptospires in both the logarithmic growth phase and the stationary phase. [29,36,41] High concentrations of tetracycline were associated with a leptospiricidal effect, which could not be attained with low concentrations of the drug. [16,39,41] Gentamicin, tobramycin and isepamicin showed reliable bactericidal effects on leptospires in both the logarithmic growth phase and the stationary phase. [15–67]

Several in vivo studies done in lower animals (experimental leptospirosis) have shown that streptomycin was more effective than others in completely removing leptospires from all tissues. [29,34,41] Although, penicillin, cephalosporins, tetracyclines and macrolides were also effective in experimental leptospirosis, small numbers of leptospires sometimes remained in the liver and kidney. [29,31,32,34,35,38,41] Recently, Truccolo et al. evaluated the susceptibility of leptospires to selected antimicrobial agents (ampicillin, doxycycline and ofloxacin) in a hamster model. [48] Their results demonstrated the ability of ampicillin at a high dose to clear leptospires from the host, except from kidneys and heart, where leptospires remained at day 6. Ofloxacin was unable to clear leptospires from blood or kidneys. With doxycycline, the clearance of leptospires occurred in 2 days in all the target organs studied, with the exception of liver, which required 3 days. The standard treatment for carrier animals has been chemotherapy by injection of streptomycin; it is an effective cure for excretion of leptospires by carriers. [1,3] A single dose of streptomycin will usually remove the chronic renal carrier state caused by pomona or other serovars. [49–52] Streptomycin has also been effectively used for acutely ill domestic animals. [1,3]

Studies on chemotherapy of leptospirosis carried out as early as 1950s through 1990s in human beings indicated a role for streptomycin and other aminoglycosides. [23,30,42] Short-term treatment with streptomycin exterminates leptospires. It has been also shown to be effective for chemophrophylaxis and is used to treat subjects who are likely to have been infected in laboratory accidents or other high-risk exposure, except in circumstances where it is contraindicated. [23,42] Gentamicin, tobramycin and isepamicin may be effective as alternatives to streptomycin. [45–47]

Figure 1 shows the clinical course of Weil’s disease in a patient treated with streptomycin beginning on the first day after onset of the illness. In this patient, the fever dropped precipitously and the causative leptospires were removed. Although the patient recovered quickly, jaundice and haemorrhage appeared after the fever subsided. [25]

Although, penicillin was effective for treating leptospirosis, the causative organism has sometimes been isolated from the blood of patients after treatment with penicillin in the febrile stage. Figure 2 shows the clinical course of a patient with leptospirosis treated with penicillin and streptomycin in the early stage. The causative organism was isolated from the blood of the patient during the time of treatment with penicillin, and afterward the patient recovered quickly, with streptomycin treatment. [25] Recently, a sequential therapy of penicillin and doxycycline on a case of severe leptospirosis was reported. [52] In this case, the patient progressed to pancytopenia despite initial penicillin therapy. The patient needed a second course of antimicrobial agent with doxycycline to improve his persistent symptoms and cytopenia.

Penicillin, cephalosporins, tetracyclines and macrolides have been widely used in the treatment of human leptospirosis. However, when these antimicrobial agents are used for the treatment of leptospirosis, long-term therapy with large doses may be required from the early stage of the disease until the appearance of antibodies. [45] Table 1 shows the clinical application of principal drugs for treatment of leptospirosis.

**Prognosis**

The mortality due to leptospirosis varies from less than 1% to more than 20%. [43] The mortality is dependent on many factors including the incriminated serovar with serovars...
**Table 1: Clinical application of principal drugs for treatment of leptospirosis**

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Route of administration</th>
<th>Daily dose</th>
<th>Duration of therapy</th>
<th>Difference of effect by the time of beginning of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>Intravenously</td>
<td>4–6 million units 4–6 times</td>
<td>ca. 7 days</td>
<td>++</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>Intravenously</td>
<td>4–8 g, 2–4 times</td>
<td>ca. 7 days</td>
<td>++</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Orally</td>
<td>1–2 g, 3–4 times</td>
<td>ca. 7 days</td>
<td>++</td>
</tr>
<tr>
<td>Cefpirome/Cefozopran/ Cefepime</td>
<td>Intravenously</td>
<td>2–4 g, 2–4 times</td>
<td>ca. 7 days</td>
<td>++</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Intramuscularly</td>
<td>1–2 g, 2 times</td>
<td>2–4 days</td>
<td>++</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Orally</td>
<td>200–400 mg, 2 times</td>
<td>ca. 7 days</td>
<td>++</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Orally intravenously</td>
<td>100–200 mg, 2 times</td>
<td>ca. 7 days</td>
<td>++</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Orally</td>
<td>2–4 g, 3–4 times</td>
<td>ca. 7 days</td>
<td>++</td>
</tr>
</tbody>
</table>

Icterohaemorrhagiae and copenhageni having the propensity to produce severe disease. The clinical spectrum of human leptospirosis ranges from mild anicteric illness to a severe illness characterized by multiple organ failure. The mild forms of leptospirosis may be much more common than the severe forms and most patients with the mild form tend to recover within 1–2 weeks. In addition to the serovar and severity of clinical spectrum, the types of clinical manifestations and complications also have a bearing on the fatality rate. Fatal outcome is mainly related to renal failure although other features such as hyperkalaemia, thrombocytopenia, cardiovascular failure with hypotension and arrhythmia, and respiratory failure with massive haemoptysis are known to contribute to the mortality rate. Neurological manifestations (e.g. disturbance of consciousness, delirium and stiffness of the neck) and digestive system symptoms (e.g. gastrointestinal bleeding, repeated nausea and vomiting, abdominal pain, meteorism and hiccups) are also associated with high mortality rate. Patient factors such as old age [Figure 3], nutritional status and presence of concomitant health problems are often associated with more severe clinical illness and increased mortality. Most deaths occur between the 10th and 15th days of illness, although death can occur as early as the fifth day of illness in fulminant severe cases [Figure 4].

If the patient is not treated for the severe form within 2–3 days after the onset of illness, it may progress in severity and sometimes be fatal. Medical professionals, especially primary care physicians, who are primarily responsible for the diagnosis and

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**Figure 1: Clinical course of a patient with Weil’s disease treated with streptomycin (SM)**

**Figure 2: Clinical course of a patient with leptospirosis treated with penicillin (PC) and streptomycin (SM)**

**Figure 3: Mortality and age group (49 fatal cases with Weil’s disease)**

**Figure 4: Death days after illness (49 fatal cases with Weil’s disease)**
treatment, need to know about the early symptoms and signs, and early clinical laboratory findings. The beginning of early pertinent antimicrobial therapy within 4–5 days after the onset of illness and proper supportive therapy and use of dialysis to treat renal failure have reduced the leptospirosis-related mortality.

References