

## Leptospirosis in Taiwan - An Underestimated Infectious Disease

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Leptospirosis is a re-emerging infectious disease affecting both animals and humans worldwide. This infection is associated with occupational contact with animals, recreational exposure and contact with leptospire as a consequence of flooding. Multiple organ involvement may be encountered in acute severe leptospirosis and early renal involvement is commonly characterized by tubulo-interstitial nephritis and tubular dysfunction. Leptospirosis has been increasingly recognized as an important infectious disease in Taiwan since 1997 and *Leptospira santarosai* serovar Shermani is the main serovar encountered. The most common presentations are fever, jaundice and acute renal failure. This triad presentation in patients with acute multiple organ dysfunction should alert physicians to the possibility of leptospirosis. Penicillin treatment is effective and may dramatically save patients from multiple organ failure provided it is given early. The rapid IgM assay may aid screening of Leptospirosis, thus allowing effective treatment to be initiated early. Leptospirosis appears to be underestimated in Taiwan and affects at least 10% of patients with multiple organ dysfunction. Therefore, a high level of clinical suspicion may help in identifying underestimated leptospirosis in Taiwan. (*Chang Gung Med J* 2007;30:109-15)



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Leptospirosis, a re-emerging infectious disease, is caused by the pathogenic spirochete leptospira.<sup>(1)</sup> This disease is transmitted directly or indirectly from animals to humans and has been deemed the most widespread zoonosis in the world, particularly in wet tropical and subtropical regions.<sup>(2,3)</sup> Infected animals urinate into water or soil. Humans are infected via wounds or by drinking contaminated water. Risk of infection occurs from occupational and recreational activities, and household environments that are in close contact with animals. Flooding is a common

precipitating factor causing outbreak or endemic leptospirosis. This disease is characterized by a broad spectrum of manifestations, which are usually sub-clinical. Its diagnosis relies upon strong suspicion of this disease from non-specific clinical presentations.

Although leptospirosis is not a major public health problem in many countries, endemic and epidemic outbreak of this disease with considerable morbidity and mortality has been reported.<sup>(4)</sup> Leptospirosis has been a neglected infectious disease in Taiwan; the first case was diagnosed in 1976.<sup>(5)</sup>

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For the past 20 years, this disease has been underestimated as an infectious disease, as well as a cause of acute renal failure, until 1997 when we reported our cases.<sup>(6)</sup> Since then an increasing number of leptospirosis cases have been identified using the veterinary diagnostic facilities at the Graduate Institute of Veterinary Medicine, National Taiwan University.<sup>(7)</sup> A national surveillance and reporting system for leptospirosis was established in 2000 by Taiwan's Center for Disease Control (CDC). Since 2004, reporting this infectious disease once it is suspected has been compulsory. This review presents the experience of leptospirosis in Taiwan.

### **Clinical manifestation of leptospirosis in Taiwan**

A broad spectrum of clinical manifestations may occur in humans, ranging from subclinical infections and self-limited anicteric febrile illnesses, to severe and potentially fatal icteric disease. Typically, the disease falls into one of four clinical categories: (i) mild influenza-like illness; (ii) Weil's syndrome characterized by jaundice, renal failure, hemorrhage and myocarditis with arrhythmias; (iii) meningitis/meningoencephalitis; and (iv) pulmonary hemorrhage with respiratory failure.<sup>(8)</sup> Leptospirosis causes multiple organ damage (kidney, liver and lung lesions) in 5%-10% of cases. Weil's syndrome is the most severe leptospirosis infection, which presents as a febrile illness with a hemorrhagic tendency, hepatic dysfunction and acute renal failure, and can be fatal if left untreated for a short period of time. In Taiwan, the most common presentations of acute leptospira infection are fever, jaundice and acute renal failure.<sup>(6,9)</sup> A triad presentation with acute multiple organ dysfunction in patients should alert physicians to the possibility of leptospirosis infection.

### **Multiple organ dysfunction**

Between 1996 and 1999, 12 patients with a mean age of  $56 \pm 13$  years (range 28-77 years) were diagnosed with severe leptospirosis at Chang Gung Memorial Hospital.<sup>(9)</sup> Among these 9 male and 3 female patients, 6 were farmers, 1 was an employee at a beef slaughterhouse and 2 raised dogs as pets at home. The principal symptoms and signs were fever (10/12), jaundice (10/12) and acute renal failure (12/12). Abdominal pain (8/12) and myalgia (7/12) were early symptoms. Six patients had splenomegaly

and 3 had hepatomegaly. Other presentations included acute respiratory failure (9/12), disturbed consciousness (6/12), hemorrhagic tendency (4/12), rhabdomyolysis (3/12), hemophagocytic syndrome (1/12) and acute pancreatitis (3/12), indicating a wide variety of leptospiral injuries to multiple organs. Biochemical study in these patients showed that the highest mean bilirubin level was  $15.2 \pm 16.1$  mg/dl (range 0.4-42.2 mg/dl), highest mean blood urea nitrogen (BUN) level was  $112.2 \pm 26.9$  mg/dl (range 74-144 mg/dl) and highest mean creatinine level was  $7.3 \pm 1.6$  mg/dl (range 4.8-9.5 mg/dl).<sup>(9)</sup>

### **Acute renal failure and thrombocytopenia**

Acute renal failure is a common phenomenon in patients with acute leptospirosis and was present in all patients in this early series. Five patients had non-oliguric and 7 patients had oliguric acute renal failure. Hypokalemia was identified in 9 patients. Among these patients, 3 required temporary intermittent hemodialysis and 1 underwent continuous venous-venous hemodialysis (CVVHD) therapy. Acute tubulo-interstitial nephritis was diagnosed by renal biopsy in 2 patients. Although leukocytosis was found in 8 patients during the course of leptospirosis, 2 patients were leukopenic. As noted in a previous study,<sup>(10)</sup> thrombocytopenia can be associated with severe endotoxin injury of leptospirosis and may appear in association with acute renal failure. In this series, thrombocytopenia occurred in 8 patients and, notably, included all 4 patients requiring hemodialysis. Three patients who required hemodialysis had severe thrombocytopenia.

### **Characteristic renal sonographic findings**

Renal sonography study at the stage of acute renal failure had characteristic findings: enlarged kidneys (means:  $12.3 \pm 1.2$  cm for the left kidney and  $12.2 \pm 1.3$  cm for the right) with relatively normal parenchymal echogenicity. These findings are compatible with pathological findings of interstitial edema.<sup>(6)</sup>

### **Pulmonary hemorrhage**

Pulmonary manifestations are common and can be the most significant feature of leptospiral infection. Manifestations include cough, dyspnea, hemoptysis and chest pain. They are primarily hemorrhagic in nature, rather than inflammatory reactions, caus-

ing severe complications in acute leptospirosis, which can even lead to adult respiratory distress syndrome and fatality.

We have reported a case of leptospirosis with initial manifestation of pulmonary hemorrhage.<sup>(11)</sup> This patient presented with rapidly developed fever, hemoptysis and severe dyspnea prior to admission. Chest radiography showed bilateral diffuse pulmonary infiltrates. Parenteral penicillin was administered immediately under the suspicion of leptospirosis and the patient recovered dramatically. The leptospira IgM test was strongly positive and the microscopic agglutination test (MAT) showed an elevated titer of 1:6400 against *Leptospira santarosai* serovar Shermani (*L. shermani*). Neither jaundice nor renal insufficiency developed. Being under-recognized in the past, leptospirosis should be added to the differential diagnosis of pulmonary hemorrhage. Early antibiotic administration effectively treats the pulmonary hemorrhage and reduces mortality.

#### **Aseptic meningitis**

Aseptic meningitis can be found in up to 25% of leptospirosis patients, particularly in the pediatric group.<sup>(12)</sup> We had a 39-year-old female patient, in a pork selling business in a market, who presented to us with high fever, chills, migrating headache and flank pain. Although brain CT and lumbar puncture did not show evidence of bacterial meningitis, dipstick IgM assay revealed a strongly positive reaction to leptospira. After doxycycline was used, the patient's headache improved dramatically.

#### **Cardiac involvement**

Cardiac involvement in leptospirosis is common and may be underestimated. Clinical evidence of myocardial involvement comprises myocarditis and abnormal T wave changes. Repolarization abnormalities<sup>(13)</sup> and arrhythmias<sup>(14)</sup> on an electrocardiogram (ECG) were considered poor prognostic indicators in severe leptospirosis cases. The presence of myocarditis was strongly correlated to severity of pulmonary symptoms in anicteric Chinese patients.<sup>(15)</sup> A leptospirosis patient with marked sinus bradycardia (40-55/min) and acute renal failure had a good response to penicillin treatment.<sup>(16)</sup>

#### **Liver involvement**

Hepatic dysfunction in leptospirosis is usually

mild and may resolve eventually. Although the liver is not the main target of spirochete infection, elevation of serum bilirubin levels may be much higher than those of aspartate transaminase (AST) and alanine transaminase (ALT) in acute viral hepatitis. In our previously reported series of 11 patients, the biochemistry changes were only mildly abnormal in the early stage.<sup>(17)</sup> However, in 3 mortality cases, the AST elevation was unusually high in the late stage. Further, significantly higher AST/ALT peak ratios (>3.0) were also noted in patients who eventually succumbed. Therefore, close follow-up of transaminases provides a useful indicator for therapeutic effectiveness in leptospirosis patients. Progressive elevation of AST without a concomitant rise of ALT likely predicts death.

#### **Renal involvement: acute tubulo-interstitial nephritis and tubular transport dysfunction**

Leptospiral endotoxins, located on the outer membrane of the bacteria, appear to be the major antigens that produce immunity to *L. interrogans* and are responsible for renal dysfunction.<sup>(18)</sup> Therefore, identification of outer membrane proteins has become a critical step in current leptospiral research. The leptospira outer membrane protein activates NF- $\kappa$ B and downstream genes expressed in medullary thick ascending limb (mTAL) cells.<sup>(19)</sup> A major pathogenic outer membrane protein LipL32 induces tubulo-interstitial nephritis-mediated gene expression in mouse proximal tubule cells.<sup>(20)</sup> LipL32 has a direct effect on proximal tubular cells to cause substantial increase of gene and protein expression of proinflammatory cytokines, such as iNOS, MCP-1, RANTES and TNF- $\alpha$ . These findings indicate the importance of LipL32 in pathogenesis, diagnosis and prevention of leptospirosis. Therefore, the outer membrane protein components of the spirochete leptospira shall continue to be a primary focus for future study.

Clinically, non-oliguric acute renal failure, hypokalemia and sodium wasting occur frequently in leptospirosis. Tubulo-interstitial nephritis with interstitial edema and mononuclear cellular infiltration are typical findings. Detailed *in vivo* tubular clearance tests, performed on 3 patients with leptospirosis (*L. shermani*) and hypokalemia, identified a defective Na(+)-K(+)-Cl(-) co-transporter and poor response to furosemide infusion due to tubular dys-

function. An *in vitro* study, using mTAL cultured cells derived from normal mice, demonstrated down-regulation of NKCC2 mRNA expression and inhibition of Na(+)-K(+)-Cl(-) co-transporter activity in mTAL cells by *L. Shermani* outer membrane protein extract. These changes may account for the observed electrolyte disorders in leptospirosis renal disorders.<sup>(21)</sup>

### **Clinical distinction of leptospirosis in multiple organ dysfunction patients**

Systemic infections from micro-organisms other than leptospira may also present multiple organ involvement and cause confusion in diagnosis of leptospirosis. A case-control study was conducted to obtain information for differential diagnosis between leptospirosis and other infections.<sup>(22)</sup> Twenty-two confirmed and 21 excluded cases of leptospirosis were identified from 169 suspected cases. The most common presentations in the confirmed group were fever (95.5%, 21/22), acute renal failure (86.4%, 19/22), myalgia (72.7%, 16/22) and jaundice (63.6%, 14/22). Ten patients were infected through occupational or recreational exposure, and 6 patients were infected as a consequence of flooding. The overall fatality rate was 4.5% (1/22). The most common presentations of the leptospirosis cases compared with those of the excluded cases were increased incidence of hemorrhagic diathesis (Odds Ratio: 10,  $p = 0.04$ ), myalgia (Odds Ratio: 8.0,  $p = 0.02$ ), bilateral enlarged kidneys (Odds Ratio: 7.5,  $p = 0.0004$ ), sterile pyuria (Odds Ratio: 6.3,  $p = 0.017$ ) and thrombocytopenia (Odds Ratio: 4.8,  $p = 0.04$ ). Treatment with penicillin was effective in the confirmed leptospirosis group. Thus, prompt recognition of leptospirosis by characteristic presentations followed by timely antibiotic treatment can dramatically reduce the mortality rate for infected patients, even in cases with severe multiple organ damage. This case-control study provides characteristics for early identification of leptospirosis that differentiate it from other infectious diseases.

### **Diagnostic methods**

Diagnosis of leptospirosis can be made by demonstration of leptospira in a clinical specimen, culture of the leptospira or a positive serology test using MAT. Serologic diagnosis is based on paired 2-week four-fold changes of titers against leptospira

serovar or a single MAT titer of more than 1:400 plus a positive leptospira IgM test. Rapid diagnosis is critical as acute leptospirosis has varied clinical manifestations and only early treatment can save patients. The MAT is a sophisticated test that cannot be performed in every laboratory. Thus, there is urgent need for an early rapid test to allow prompt clinical diagnosis and treatment.

IgM antibody for leptospira can be detected on days 6 to 10 after disease onset, peaks within 3-4 weeks and remains detectable for months to years. An easy and rapid Lepto IgM assay used to assess acute leptospirosis achieved good sensitivity and specificity. High titer of MAT ( $\geq 1:400$ ) correlates well with positive rates of IgM. Therefore, this test is suitable for use at the peripheral level as a rapid screening test for early diagnosis of leptospirosis. From September 2000 to August 2005, 441 patients with multiple organ dysfunction underwent screening with an IgM Leptospira dipstick assay (Panbio, USA) and a Leptotek lateral flow (bioMerieux, France), and leptospirosis was confirmed in forty-one patients (9.3%). Leptospirosis thus proved to be a salient cause of multiple organ dysfunction.

### **Treatment: penicillin saves patients from mortality**

There is evidence of the effectiveness of early antibiotic treatment for leptospirosis.<sup>(23)</sup> High doses of intravenous penicillin have been recommended for severe cases but oral antibiotics, such as doxycycline, amoxicillin, ampicillin or erythromycin, can be used for less severe cases. Third-generation cephalosporins also appear to be effective. Jarisch-Herxheimer reactions may occur following effective treatment. Although leptospira is shown to be sensitive to a wide range of antibiotics in *in vitro* and animal experiments, there is limited clinical experience with the newer antibiotics.

Early intravenous penicillin administration in leptospirosis patients provides favorable results. In our early series, 8 out of 12 patients survived and 7 out of 8 of those patients were saved from severe multiple organ failure. One surviving patient received tetracycline treatment for relatively mild leptospirosis.<sup>(9)</sup> In a second series, which used case control for leptospirosis, confirmed leptospirosis cases received penicillin treatment (3 million units, intravenously every six hours). Serum creatinine lev-



els of confirmed cases improved in a mean of  $2.7 \pm 2.2$  days.<sup>(22)</sup> Therefore, treatment with effective antibiotics should be initiated as soon as a diagnosis of leptospirosis is suspected and preferably before day 5 after illness onset. Although the benefit of antibiotics after day 5 is controversial, most clinicians employ antibiotics regardless of the illness onset date. Clinicians should never wait for laboratory test results before initiating therapy with antibiotics as serological test results do not become positive until about a week after the onset of illness, and cultures may not become positive for several weeks.

### National surveillance

Before the Taiwan CDC surveillance system was established, sera of suspected leptospirosis patients (1996-1999) were studied at the Graduate Institute of Veterinary Medicine, National Taiwan University. Of all 169 sera samples collected during that period of time, leptospira seropositive (MAT > 1:100) was proved in 79 patients (46.7%) and 18 patients (10.8%) were considered probable (MAT > 1:400). *L. shermani* occurred in 72.2% of patients. Since the Taiwan CDC national surveillance and reporting system started to function in April 2000, 1,632 suspected cases have been reported up to December 2002. Among these cases, 251 were seropositive and 88 cases were probable positive infection based on sera analysis. There were 57 cases finally confirmed as leptospirosis.<sup>(24)</sup> The mean age in these confirmed cases was 45 years. There were 51 males (89.47%) and 6 females (10.53%). The principal serovar was *L. shermani* (56.14%, 32/57). Among 240 serovars, *L. shermani* was the main infecting serovar, followed by *L. bratislava*, *L. balum*, and *L. copenhageni* in Taiwan.<sup>(24)</sup> The number of reported and confirmed cases of leptospirosis has continued to increase after the establishment of the national surveillance system.

### Typhoon and flooding

In September 2001, Typhoon Nali hit northern Taiwan and caused severe flooding. This flood was followed by an outbreak of leptospirosis in October 2001 with 16 confirmed cases. The onset of this outbreak was compatible with the flooding for incubation time and contact history. All these patients presented with multiple organ dysfunction. Besides fever, acute renal failure was the most distinct mani-

festation of leptospirosis. There was only one mortality, as these patients were treated with appropriate antibiotics under clinical alertness for leptospirosis. Therefore, a high level of clinical suspicion regarding acute renal failure and other characteristic symptoms may help in identifying leptospirosis in patients with multiple organ dysfunction in Taiwan.

### Conclusion

The incidence of leptospirosis is underestimated in Taiwan. Clinical manifestations vary from mild to severe. The most common presentations in severe cases are fever, jaundice and acute renal failure. This triad presentation in patients should alert physicians to the possibility of leptospirosis. The Lepto IgM assay may aid early diagnosis. When leptospirosis is clinically suspected, treatment with appropriate antibiotics should be initiated immediately.

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## 鈎端螺旋體感染在台灣——一個被低估的感染疾病

楊智偉

鈎端螺旋體病是國際上重視之再浮現人畜共通感染疾病。職業接觸、野外活動及水災與鈎端螺旋體菌接觸而常造成感染。部分急性鈎端螺旋體感染易引起多重器官病變，並常見急性腎衰竭合併腎小管間質腎炎與腎小管機能障礙。台灣自 1997 年以來，鈎端螺旋體感染已愈來愈被認為是台灣重要感染性疾病，而最常見之血清型為 *Leptospira santarosai* serovar *Shermani*。鈎端螺旋體感染最常見的臨床表徵為發燒、黃疸及急性腎衰竭。多重器官病變之病患若有以上三種表徵合併出現，則需考慮鈎端螺旋體感染。青黴素可以很有效治療多重器官病變之鈎端螺旋體感染病患。一些快速 IgM 診斷的方法，則可協助早期治療鈎端螺旋體感染。台灣鈎端螺旋體感染是被低估之感染疾病，估計多重器官病變之病患大約有 10% 是鈎端螺旋體感染。因此，臨床的高度警覺，可以協助發現更多鈎端螺旋體感染之病患及早診斷與治療。(長庚醫誌 2007;30:109-15)

**關鍵詞：**鈎端螺旋體感染，急性腎衰竭

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