# CLINICAL PRESENTATION AND MEDICAL COMPLICATION IN 59 CASES OF LABORATORY-CONFIRMED LEPTOSPIROSIS IN BANGKOK

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**Abstract.** We reviewed the laboratory-confirmed cases of leptospirosis in Ramathibodi Hospital, a medical-school hospital in Bangkok, to assess the documented cases of leptospirosis in Bangkok and the medical complications of severe cases. There were 59 cases from January 1994 to December 2000. More than half of the cases were Bangkok residents and did not travel outside Bangkok in the preceding 2 weeks. The majority of the cases presented in late rainy season. The clinical presentation, laboratory findings, medical complication, treatment and outcome are given. Leptospirosis in the urban area is common and should be recognized, particularly in rainy season.

## INTRODUCTION

Leptospirosis is a spirochetal zoonosis that causes a wide spectrum of clinical manifestations in humans. The syndromes include subclinical infection, self-limited anicteric febrile illness, and a severe and potentially fatal illness known as Weil's syndrome (Sundharagiati *et al*, 1966; Feigin and Anderson, 1975; Levett 2001; Vinetz, 2001). Leptospirosis is distributed worldwide but it is more common in tropical climates (Lomar *et al*, 2000; Levett, 2001; Vinetz, 2001). Recently, the incidence in Thailand is high and leptospirosis is considered an important re-emerging infectious disease (Panaphut *et al*, 2002). The majority of the cases are in the rural area particularly in the northeastern part of Thailand. The documented cases in Bangkok residents are rare (Heisey *et al*, 1988; Kiatboonsri *et al*, 1995). Ramathibodi Hospital, a medical-school hospital in Bangkok, provides medical services to patients who live or work in Bangkok and some of the cases are referred from the other provinces. We present the clinical features, laboratory findings, medical complications, treatment and outcome in these cases.

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## MATERIALS AND METHODS

All of the cases identified as leptospirosis in the medical record from January 1994 to December 1999 were reviewed. Only the cases with serologically proven by indirect hemagglutination assay (IHA), negative blood culture for bacteria, and no other identified causes for the illness were included into this study. The data including demographic data, clinical manifestation, laboratory findings, medical complication, treatment, and outcome were studied.

## RESULTS

There were 59 cases of leptospirosis and 50 cases (84.7%) were male. The distribution of the patients' age and the month of presentation are shown in Fig 1 and Fig 2, respectively. The majority of the cases (62.7%) presented in late rainy season (August-November). Thirty-four cases (57.6%) were Bangkok residents and had no history of traveling outside Bangkok in the previous 2 weeks. Ten cases (16.9%) were people who worked in Bangkok and had visited the northeastern part of Thailand in the preceding 2 weeks. The others (15 cases, 25.5%) were people who lived in nearby provinces and the central part of Thailand (Samut Prakan 4; Nonthaburi 3; Ratchaburi 3; Ayutthaya 2, Saraburi 1; Sing Buri 1; Kanchanaburi 1).

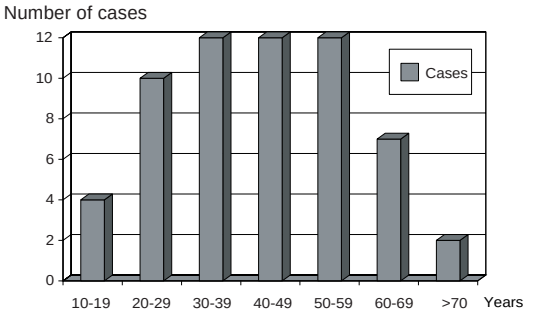


Fig 1–Age distribution of 59 cases of leptospirosis.

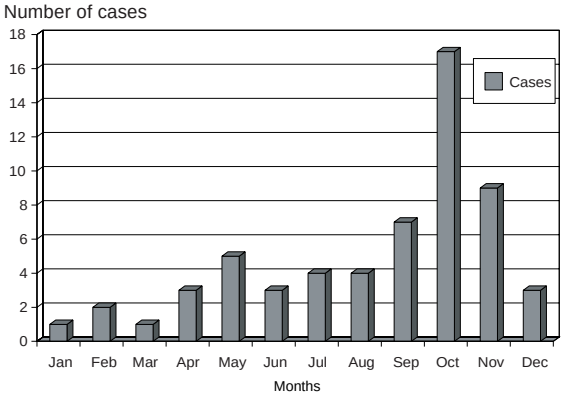


Fig 2–Distribution of the month presented in 59 cases of leptospirosis.

Fifty-one cases (86.4%) had been recorded about the history of disease exposure in the files. Twenty-six from 51 cases (51.0%) had been exposed to contaminated water (walking through stagnant water in urban or rural area, or working in rice fields); five cases (9.8%) had been exposed to rats (seeing in house or being bitten); the others (20 cases, 39.2%) had no suspicious exposure. The duration from suspicious exposure to onset of illness ranged from 7 to 15 (mean 10.4) days.

Clinical presentation and laboratory findings of the patients were categorized in icteric and anicteric groups, as shown in Table 1 and Table 2, respectively. Forty-five cases (76.3%) had the diagnosis confirmed by single leptospira titer (1:80-1:640); the others needed a four-fold rising titer in the second serum sample. Urine examination for the spirochete by dark field microscope revealed positive result in 2 from 7 cases (28.6%). Medical complications were found mainly in icteric cases (Table 3). All of the cases were treated with antimicrobial drugs and supportive care. Antimicrobial drugs used were: penicillin (17 cases, 28.8%),

Table 1
Clinical presentation in 59 cases of leptospirosis.

| Symptoms/signs | Icteric cases (n = 41) | | Anicteric cases (n = 18) | | All cases (n = 59) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Fever | 40 | 97.6 | 18 | 100 | 58 | 98.3 |
| Myalgia | 30 | 73.2 | 12 | 66.7 | 42 | 71.2 |
| Hepatomegaly | 23 | 56.1 | 8 | 44.4 | 31 | 52.5 |
| Headache | 18 | 43.9 | 11 | 61.1 | 29 | 49.2 |
| Vomiting | 18 | 43.9 | 4 | 22.2 | 22 | 37.3 |
| Conjunctival suffusion | 17 | 41.5 | 11 | 61.1 | 28 | 47.5 |
| Chill | 16 | 39.0 | 8 | 44.4 | 24 | 40.7 |
| Oliguria | 14 | 34.1 | 7 | 38.9 | 21 | 35.6 |
| Calf tenderness | 14 | 34.1 | 2 | 11.1 | 16 | 27.1 |
| Diarrhea | 13 | 31.7 | 4 | 22.2 | 17 | 28.8 |
| Cough | 12 | 29.3 | 3 | 16.7 | 15 | 25.4 |
| Alteration of consciousness | 9 | 21.9 | 6 | 33.3 | 15 | 25.4 |
| Lymphadenopathy | 5 | 12.2 | 1 | 5.6 | 6 | 10.2 |
| Petichiae | 5 | 12.2 | 3 | 16.7 | 8 | 13.6 |
| Nuchal rigidity | 4 | 9.8 | 3 | 16.7 | 7 | 11.9 |
| Splenomegaly | 3 | 7.3 | 1 | 5.6 | 4 | 6.8 |
| Epistaxis | 3 | 7.3 | - | - | 3 | 5.1 |
| Hemoptysis | 1 | 2.4 | - | - | 1 | 1.7 |
| Seizure | 1 | 2.4 | - | - | 1 | 1.7 |

Table 2
Laboratory findings in 59 cases of leptospirosis.

| Symptoms/signs | Icteric cases (n = 41) | Anicteric cases (n = 18) |
|---|---|---|
| **CBC and blood chemistries** | Mean ± SD | Mean ± SD |
| Hb (g/dl) | 11.6 ± 2.4 | 12 ± 2.37 |
| Hct (%) | 33.6 ± 6.4 | 36.4 ± 7.1 |
| WBC (cells/$mm^3$) | 15,600 ± 6,007.3 | 14,300 ± 7,280.2 |
| Platelets (cells/ $mm^3$) | 14,300 ± 7,280.2 | 128,000 ± 77,863.1 |
| BUN (mg/dl) | 68.7 ± 27.3 | 36.7 ± 12.6 |
| Cr (mg/dl) | 5.6 ± 3.4 | 2.1 ± 0.8 |
| Uric acid (mg/dl) | 8.46 ± 0.2 | 6.7 ± 3.4 |
| $HCO_3$ (mmol/l) | 17 ± 6.3 | 21 ± 4.9 |
| AST (U/l) | 106 ± 64.7 | 42 ± 21.3 |
| ALT (U/l) | 98 ± 48.3 | 48.5 ± 23.1 |
| TB (mg/dl) | 12 ± 8.6 | 1.39 ± 0.42 |
| DB (mg/dl) | 9.2 ± 5.3 | 0.7 ± 0.2 |
| ALP (U/l) | 117 ± 63.8 | 96 ± 45.3 |
| CPK (U/l) | 3,011 ± 1,424.1 | 103 ± 52.3 |
| **Urine analysis** | Case (%) | Case (%) |
| Proteinuria ( ≥ 1+) | 38 (92.7) | 12 (66.6) |
| WBC ≥ 5 cells/HPF | 32 (78.0) | 11 (61.1) |
| RBC ≥ 5 cells/HPF | 33 (80.4) | 8 (44.4) |
| Cellular cast | 31 (75.6) | 6 (33.3) |
| **Chest radiography** | Case (%) | Case (%) |
| Normal | 11/38 (28.9) | 11/16 (68.8) |
| Abnormal | 27/38 (71.1) | 5/16 (31.2) |
| Interstitial infiltration | 9/38 (23.7) | 4/16 (25.0) |
| Alveolar infiltration | 5/38 (13.2) | - |
| Pulmonary edema | 12/38 (31.6) | - |
| Pleural effusion | 1/38 (2.6) | - |

AST = aspartate aminotransferase; ALT = alanine aminotransferase; TB = total bilirubin; DB = direct bilirubin; ALP = alkaline phosphatase; CPK = creatinine phosphokinase

amoxycillin (9 cases, 15.3%), ceftriaxone or cefotaxime (22 cases, 37.3%), and doxycycline (11 cases, 18.6%). Dialysis and respirator support were needed in 13 (31.7%) of the icteric cases. Majority of the cases (56 cases, 94.9%) had complete recovery. Mortality rate was 5.1% (3 cases).

## DISCUSSION

Leptospirosis in human is acquired by contact with urine or tissues of an infected animal or through contaminated water and soil (Sasaki *et al*, 1993; Tangkanakul *et al*, 2000). The high incidence in endemic area emphasizes the need for physicians to aware of this illness and for the diagnosis to be sought. However, the cases in an urban area like Bangkok particularly those without prior suspicion are often questioned and sometimes result in delayed or missed diagnosis. Our study demonstrates the documented cases in Bangkok residents since over half of the cases live in Bangkok and have no history of traveling outside. A previous animal surveillance study

Table 3
Medical complications in 59 cases of leptospirosis.

| Symptoms/signs | Icteric cases (n = 41) No. (%) | Anicteric cases (n = 18) No. (%) |
|---|---|---|
| Acute renal failure (Cr > 2.5) | 35 (85.4) | 9 (50.0) |
| Need dialysis | 13 (31.7) | - |
| Hypotension (BP < 90/60) | 14 (34.1) | - |
| Pulmonary edema | 12 (29.3) | - |
| Need respirator support | 6 (14.6) | - |
| ARDS | 7 (17.1) | - |
| Pulmonary hemorrhage | 4 (9.8) | - |
| Upper GI bleeding | 13 (31.7) | 1 (5.6) |
| Rhabdomyolysis | 6 (14.6) | - |
| Acute pancreatitis | 4 (9.8) | - |
| Aseptic meningitis | 4 (9.8) | 3 (16.7) |
| Myocarditis | 2 (4.9) | - |
| Coagulopathy | 2 (4.9) | - |

in Thailand indicates that rats and dogs can be the source of human leptospirosis infection in both urban and rural areas (Heisey *et al*, 1988). Nearly forty percents of the cases in our study had no suspicious exposure. Thus, leptospirosis should not be excluded in patients who live in urban area or have no history of suspicious exposure.

Epidemiological results show that the distribution of age and the months presented are similar to previous reports in endemic rural areas (Tangkanakul *et al*, 2000; Panaphut *et al*, 2002). The most common clinical presentation involved nonspecific signs or symptoms, including fever, myalgia, hepatomegaly, and headache which is consistent with the results from a large-scale study of clinical presentation including 353 patients in Hawaii (Katz *et al*, 2001). However, conjunctival suffusion, a suggestive sign of leptospirosis, in our study and a previous study in Khon Kaen, Thailand (Panaphut *et al*, 2002) was much higher that that in Katz *et al* (2001) study (47.5-52.9% compared to 28%). Conjunctival suffusion should be a good suggestive sign of leptospirosis in Thailand. In contrast, calf muscle tenderness, another suggestive sign of leptospirosis, is found in only one-fourth of the cases.

Because early recognition and initiation of antibiotic therapy are important, clinicians should familiarize themselves with the clinical presentation of leptospirosis, and when evaluating a febrile patient with myalgia, hepatomegaly, headache, and particularly with conjunctival suffusion and/or calf muscle tenderness, they should have leptospirosis in the differential diagnosis.

Multiple organ involvement may be encountered in leptospirosis, and early renal involvement is very common, characterized by tubulo-interstitial nephritis and tubular dysfunction (Yang *et al*, 2001). In our study, acute renal failure was a common clinical feature in both icteric and anicteric cases. However, only some icteric cases needed dialysis and all had complete recovery. Proteinuria, an early finding mentioned by Kobayashi (2001) was found in nearly all (92.7%) icteric cases and two-thirds of anicteric cases in our study. Furthermore, pyuria, microscopic hematuria, and cellular casts were found in a majority of cases. These findings can promptly lead to the diagnosis of leptospirosis in addition to suspicious clinical features.

Two-thirds of icteric cases and one-third of anicteric cases had abnormal chest radiog-

raphy. Interstitial infiltration (Andreescu *et al*, 1999) was found in one-fourth of both icteric and anicteric cases. Pulmonary hemorrhage, a lethal complication of leptospirosis, has become more widely recognized (Vinetz, 2001) and presents as alveolar infiltration (Martinez *et al*, 2000; Matos *et al*, 2001).

Aseptic meningitis is a medical complication that was only found in anicteric cases in our study. All of these cases were confirmed by lumbar puncture and CSF analysis. Aseptic meningitis in anicteric cases is an important clue that can lead to the diagnosis. It commonly occurs in the second week of illness and usually has completed recovery (Sperber and Schleupner, 1989; Watt *et al*, 1989).

Almost all medical complications occur in icteric cases, as is widely recognized. Rhabdomyolysis, pancreatitis, and myocarditis, rare but life-threatening (Ramachandran and Perera, 1977; de Brito *et al*, 1987; Coursin *et al*, 2000), were found in 14.6%, 9.8%, and 4.9%, respectively. Leptospirosis should be considered in the evaluation of a patient with clinical sepsis who develops multiple organ dysfunction associated with rhabdomyolysis.

Coagulopathy was found in 2 cases (4.9%). However, there was no clinical bleeding in these cases. A previous study of coagulation function in cases with leptospirosis showed slight changes in coagulation factors (Jaroonvesama *et al*, 1975). This finding suggests that the damage of capillary endothelium was more pronounced than coagulopathy which may be due to liver cell damage.

Indirect hemagglutination assay is a good serology test which had high accuracy (sensitivity 92.2%, specificity 94.4%, positive predictive value 95.9%, and negative predictive value 92.7%) (Levett *et al*, 2001). In our study, only three-fourth of the cases had a positive initial serum finding; the others need the second serum sample to show a 4-fold rise. The limitation of our study was that we could not evaluate the accuracy of this test in clinical setting since we included only cases confirmed by this test.

Through dark field microscopy looking for leptospires in urine was performed by our experienced personnel, only 2 from 7 cases revealed positive results. This investigation may not be a good diagnostic tool for leptospirosis. Vijayachari *et al* (2001) has evaluated dark field microscopy as a diagnostic tool for leptospirosis in 170 patients and found that the accuracy was quite low (sensitivity 40.2%, specificity 61.5%, positive predictive value 55.2%, and negative predictive value 46.6%).

Antibiotic regimens for the treatment of leptospirosis is a form of care for which the evidence is insufficient to provide clear guidelines for practice (Guidugli *et al*, 2000). Randomized trials suggest that antibiotics could be a useful treatment for leptospirosis. Initiation of antibiotics before the seventh day of symptoms was associated with a significantly shortened duration of illness (Katz *et al*, 2001; Levett, 2001). Of a variety of antibiotics used, penicillins and cephalosporins have the lowest minimal inhibitory concentration against leptospires (Kobayashi, 2001). In our study, ceftriaxone or cefotaxime was used in patients in whom bacterial sepsis was suspected. Unfortunately, we cannot evaluate the efficacy of each antimicrobial drug due to the limited number of cases.

Death occured in about 5% of the patients in a systemic review (Guidugli *et al*, 2000). Three patients (5.1%) in our study died due to intractable shock and pulmonary hemorrhage. In addition to oliguria which is well recognized as an independent, poor prognostic factor (Daher *et al*, 1999), hypotention and pulmonary hemorrhage are also associated with significant mortality (Bethlem and Carvalho, 2000; Panaphut *et al*, 2002).

In conclusion, leptospirosis is documented in Bangkok residents. Leptospirosis should not be excluded in patients who live in the urban area or have no history of suspicious exposure. Renal and pulmonary involvement present in a majority of both icteric and anicteric cases. Urinalysis and chest radiography are helpful for the early provisional diagnosis. In addition to acute renal failure and pulmonary involvement, rhabdomyolysis, acute pancreatitis, aseptic

meningitis, myocarditis are life-threatening medical complications.

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