Clinical presentation of leptospirosis: a retrospective study of 201 patients in a metropolitan city of Brazil

ABSTRACT

Introduction: leptospirosis is a zoonosis of worldwide importance. The disease is endemic in Brazil. This study was conducted to describe the clinical and laboratory presentation of leptospirosis in a metropolitan city of Brazil. **Methods:** this is a retrospective study including 201 consecutive patients with leptospirosis admitted to tertiary hospitals in Fortaleza, Brazil, between 1985 and 2006. All patients had clinical and epidemiological data suggestive of leptospirosis, and positive laboratorial test for leptospirosis (microscopic agglutination test, MAT, higher than 1:800). **Results:** a total of 201 patients were included, with mean age of 38.9 ± 15.7 years; 79.1% were male. The mean length from onset of symptoms to admission was 7 ± 3 days. The main clinical signs and symptoms at admission were fever (96.5%), jaundice (94.5%), myalgia (92.5%), headache (74.6%), vomiting (71.6%) and dehydration (63.5%). Hemorrhagic manifestations were present in 35.8%. Acute kidney injury was found in 87% of the patients. Platelet count was less than 100,000/mm^3 in 74.3%. Hematuria was found in 42.9%. Death occurred in 31 cases (15.4%). **Conclusions:** leptospirosis is a globally relevant disease with potential fatal outcome. Signs and symptoms suggestive of leptospirosis must be known by any physician in order to institute early adequate treatment to improve outcome. Early indication and daily hemodialysis seems to be beneficial in this group of patients.

Keywords: leptospirosis, clinical manifestations, laboratory findings, mortality.

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INTRODUCTION

Leptospirosis is a worldwide zoonotic disease caused by pathogenic leptospires belonging to the *Leptospira spp*. genus that affects predominantly men. The incidence of human infection is higher in the tropics than in temperate regions.[1-3] Human infection results from exposure to infected urine of carrier mammals, either directly or via contamination of soil or water. Leptospirosis is associated with occupational and recreational activities.[4-6]

Most infected subjects by *Leptospira* have asymptomatic infection or present mild symptoms, especially in endemic areas. Leptospirosis typically has two clinical forms: anicteric and icterohaemorrhagic. Fever, chills, headache, severe myalgia, conjunctival suffusion, anorexia, nausea, vomiting, and malaise usually characterizes acute leptospirosis.[7-9]

Pulmonary involvement and acute kidney injury are the main causes of death in leptospirosis.[10-12] Renal involvement in leptospirosis is characterized by acute interstitial nephritis that may be associated with acute tubular necrosis. Predisposition to hypokalemia is another particular feature of renal involvement in this disease.[13]

The present study describes the clinical and laboratory findings of patients with leptospirosis admitted to tertiary hospitals in Brazil.

METHODS

A retrospective study was conducted with 201 consecutive patients with confirmed diagnosis of leptospirosis admitted to the Walter Cantídio University Hospital and São José Infectious Diseases Hospital, in Fortaleza city, a metropolitan area in Northeast Brazil, from May 1985 to December 2006. All patients had clinical and epidemiological data suggestive of leptospirosis, and 75% of them had positive test for leptospirosis (microscopic agglutination test, MAT, higher than 1:800).

Time between onset of symptoms and admission, length of hospital stay, treatment, need of dialysis and complications were analyzed. Severity of disease was analyzed through clinical and laboratory findings. Clinical investigation included a record of all signs and symptoms

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presented by each patient, as well as arterial systolic and diastolic blood pressure at hospital admission. Laboratory data included an assessment of serum urea, creatinine, potassium, bilirubin, transaminases, creatinokinase, lactate dehydrogenase, total blood count and prothrombin time.

Severity was considered if acute kidney injury and jaundice were present at admission.

Hemorrhagic phenomena as gastrointestinal hemorrhage, hemoptysis and epistaxis were recorded at admission and during hospitalization. Respiratory insufficiency was defined as need of mechanical ventilation. Acute kidney injury (AKI) was defined according to RIFLE criteria.[14]

Although controversial, antibiotic therapy was used in some patients. Penicillin G was administered at a dosage of 8 million units/day in the first 7 to 10 days after admission.

Dialysis was indicated in those patients that remained oliguric after effective hydration, in those cases where uremia was associated with hemorrhagic phenomena or severe respiratory failure. During the period of 1985 to 1996 the type of dialysis indicated was intermittent peritoneal dialysis (IPD) but in case of extreme hypercatabolic state, where the removal of urea was inadequately and in hemodynamically unstable patients, classic hemodialysis or continuous slow hemodialysis was indicated. During the period of 1997 to 2006 only daily hemodialysis was performed.

The study protocol was reviewed and approved by the Ethical Committee of the Institutions.

Statistical analysis

The results were expressed through tables and summary measures (mean ± standard deviation) in the cases of quantitative variables. Statistical analysis was performed through the softwares SPSS 10.0 (SPSS Inc. Chicago, IL, USA) and Epi Info, 6.04b, 2001 (Centers for Disease Control and Prevention, USA). The Student's t test, Fisher's exact test and Wilcoxon test when appropriate. The descriptive values below 5% (p value < 0.05) were considered statistically significant.

RESULTS

A total of 201 patients were included, with a mean age of 38.9 ± 15.7 years old (range 8 to 84 years). There were 159 (79.1%) males. The main occupations were farmer (12.6%), student (11.6%), housemaid (11.1%) and mason (10%). Twenty eighty percent had occupations considered at high risk for leptospirosis. The mean length between the onset of symptoms and hospital admission was 7.1 ± 3.2 days (range 1 to 28 days). Almost 30% reported exposure to rats before the onset of symptoms and all the patients referred contact with stagnant water in the week prior to admission. The average period of hospital stay was 11.0 ± 7.1 days (range 0 to 42 days).

Seventy five percent of patients had serological tests higher than 1:800. Microagglutination test was positive for antibodies reactive with serovars *Icteroaemorrhagia*e in 100%, *Copenhageniin* 59%, *Cynopteri, Javanica, Djasiman* and *Pyrogenes* in 9% each.

The main signs and symptoms presented at admission were fever (96.5%), jaundice (94.5%), myalgia (92.5%), headache (74.6%), vomiting (71.6%), dehydratation (63.5%) and chills (62.2%), as summarized in Table 1. Oliguria was found in 31.8%. Hemorrhagic manifestations were present in 35.8%, including petechias (20.4%), hemoptysis (13.4%) and hematemesis (12.9%).

Table 1. Clinical findings presented by patients with leptospirosis in Fortaleza, Brazil

	n = 201
Age (years)	38.9 ± 15.7
Gender	
Male, n (%)	159 (79.1%)
Female, n (%)	42 (20.9%)
Onset of symptoms to admission (days)	7.1 ± 3.2
Length of hospital stay (days)	11.0 ± 7.1
History of contact with rats	29.8
Admission mean blood pressure	
SBP (mmHg)	108.9 ± 20.7
DBP (mmHg)	67.1 ± 14.8
Pulse (bpm)	101.6 ± 17
Signs and symptoms	
Fever	96.5
Jaundice	94.5
Myalgia	92.5
Headache	74.6
Vomiting	71.6
Dehydratation	63.1
Chills	62.2
Calf pain	51.7
Diarrhea	42.3
Hepatomegaly	37.8
Anorhexia	37.3
Oliguria	31.8
Tachypneia	32.3
Dyspnea	28.3
Crackles or rhonchi	22.9
Petechias	20.4
Arthralgias	19.9
Hemoptysis	13.4
Hematemesis	12.9
Conjunctival suffusion	11.9
Edema	11.4
Desorientation	9.4
Flapping	5.4
Constipation	4.9
Splenomegaly	2.9
Seizure	1.0
Dialysis (%)	50.7
Dialysis sessions (n)	3.2 ± 2.7
Death (%)	15.4

Mean ± SD or %. SBP - systolic blood pressure, DBP - diastolic blood pressure.

Acute kidney injury was found in 87% of the patients and 63.7% had serum potassium lower than 3.5mEq/L. Serum urea and creatinine had significantly increased during the course of the disease (172.0 ± 90.6 vs. 193.2 ± 91.2, p < 0.0001; 5.0 ± 2.9 vs. 5.5 ± 2.9, p < 0.0001, respectively). There was significant decrease of serum potassium between the admission and minimal value during hospital stay (3.8 ± 1.2 vs. 3.3 ± 0.7, p = 0.0028).

Laboratory tests showed white blood count 14,370 ± 9,010/mm^3 and platelet count 77,250 ± 67,920/mm^3; 69.8% had white blood count higher than 10,000/mm^3 and 74.3% had platelet count lower than 100,000/mm^3. Direct and indirect bilirubin were 13.5 ± 9.8 and 5.6 ± 5.2 mg/dL, respectively, and 85% presented direct bilirubin higher than 3.5 mg/dL. Aspartate amino transaminase (AST) was 112.3 ± 106.4 IU/L and alanine amino transaminase (ALT) 88.5 ± 110.7 IU/L. The AST and ALT levels were higher than 40IU/L in 82.4 and 72.1% of the patients, respectively. Creatine phosphokinase was 702.1 ± 2638 IU/L in admission and higher than 195 IU/L in 43.1%. Lactate dehydrogenase was 693.7 ± 418.1 IU/L at admission and it had significantly increased during hospital stay (p = 0.0077). Urinalysis found hematuria in 42.9%. Laboratory findings are shown in Tables 2 and 3.

Table 2. Laboratory findings during hospital stay in patients with leptospirosis in Fortaleza, Brazil

Laboratory findings	Patients with data	Mean ± SD or %	p
Hematocrit (%)	183	32.5 ± 6.0	
Hemoglobin (g/dL)	181	10.6 ± 1.9	
White blood count (x10^3/mm^3)	159	14.37 ± 9.01	
Platelet count (x10^3/mm^3)	156	77.25 ± 67.92	
Serum sodium (mEq/L)			
Maximal	196	135.4 ± 11.7	
Minimal	190	130.1 ± 11.1	< 0.0001(2)
Serum potassium (mEq/L)			
Initial	189	3.8 ± 1.2	
Minimal	193	3.3 ± 0.7	0.0028(1)
Serum urea (mg/dL)			
Initial	159	172.0 ± 90.6	
Maximal	166	193.2 ± 91.2	< 0.0001(1)
Serum creatinine (mg/dL)			
Initial	192	5.0 ± 2.9	
Maximal	201	5.5 ± 2.9	< 0.0001(1)
Serum calcium (mmol/L)	60	8.0 ± 1.9	
Serum phosphorus (mmol/L)	49	3.8 ± 1.0	
Serum clorum (mmol/L)	32	103.1 ± 11.7	
Prothrombin time (%)	58	59.3 ± 30.0	
AST (IU/L)	164	112.3 ± 106.4	
ALT (IU/L)	165	88.5 ± 110.7	
Direct bilirrubin (mg/dL)	160	13.5 ± 9.8	
Indirect bilirrubin (mg/dL)	162	5.6 ± 5.2	
Lactate dehydrogenase (IU/L)			
Initial	67	693.7 ± 418.1	
Maximal	79	694.2 ± 422.9	0.0077(2)
Creatine phosphokinase (IU/L)			
Initial	56	702.1 ± 2638.0	
Maximal	58	625.6 ± 2593.8	0.1088(2)
Blood pH	102	7.37±0.06	
Blood HCO3 (mEq/L)	89	19.49±4.88	
Urinanalysis			
pH	110	5.7 ± 0.7	
Haematuria	175	42.9%	
MAT	106	75.5%	

% or Mean ± SD. (1) Student's t-test, (2) Wilcoxon test. Initial, maximal and minimum value during hospital stay. AST - aspartate amino transaminase, ALT - alanine amino transaminase, HCO3 - bicarbonate, MAT - microscopic agglutination test (Cut-off > 1:800).

Table 3. Laboratory abnormalities in patients with leptospirosis in Fortaleza, Brazil

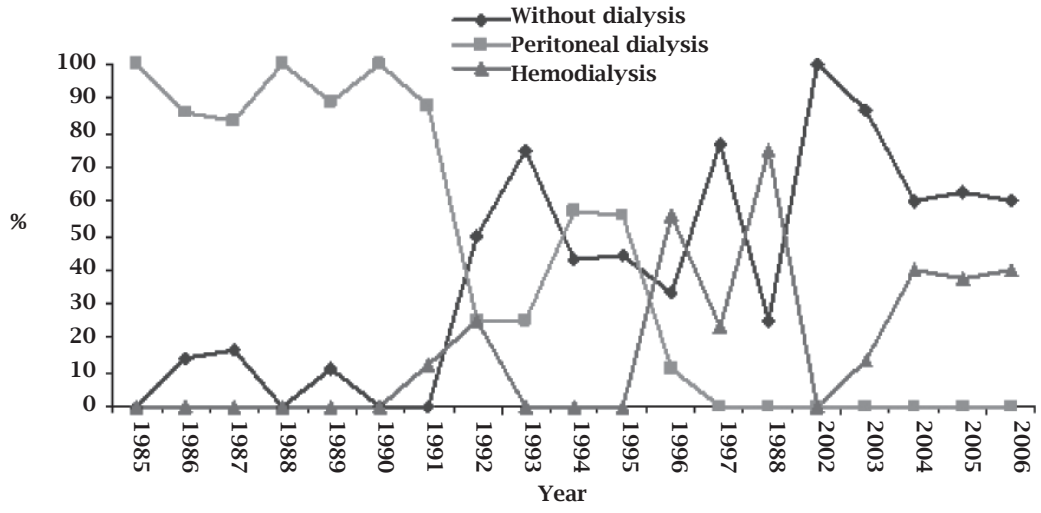
Laboratory findings	Patients with data	n (%)
Haemoglobin < 12 g/dL	181	133 (73.4%)
White blood count > 10,000/mm^3	159	111 (69.8%)
White blood count < 4,000/mm^3	159	2 (1.2%)
Platelets < 100,000mm^3	156	116 (74.3%)
Acute kidney injury	201	175 (87.0%)
K < 3.5 mEq/L	193	123 (63.7%)
Direct bilirrubin > 3.5 mg/dL	160	136 (85.0%)
AST > 40 IU/L	164	136 (82.4%)
ALT > 40 IU/L	165	119 (72.1%)
Prothrombin Time < 60%	58	20 (34.4%)
CPK > 195 IU/L	58	25 (43.1%)

K - potassium, AST - aspartate amino transaminase, ALT - alanine amino transaminase, CPK - creatine phosphokinase.

Table 4. Type of dialysis for patients with leptospirosis in the last 20 years – comparison of survivors and nonsurvivors

	Survivors (n = 86)	Non-survivors (n = 17)	p
Peritoneal dialysis	49 (57.0%)	14 (82.4%)	0.04
Hemodialysis	37 (43.0%)	3 (17.6%)	0.04
Use of antibiotics	80 (93.0%)	13 (76.4%)	0.09
Fisher's exact test			

Figure 1: Leptospirosis patients without dialysis, with peritoneal dialysis and with hemodialysis in the last 20 years.



Complications observed during hospital stay were pulmonary bleeding (14%), gastrointestinal bleeding (13%), atrial fibrillation (11.4%), pulmonary infection (6.0%), meningitis (1.0%) and pancreatitis (0.5%).

Antibiotic therapy with Penicillin G was administered in 131 (65%) of the patients, 38 (44.7%) of them between 1985 and 1996 and 93 (80.1%) between 1996 and 2006. Jarisch-Herxheimer's reaction was not seen in these patients.

Dialysis was required for 103 cases (51.2%). The mean number of dialysis sessions was 3.2 ± 2.7 sessions. Among the patients submitted to dialysis, intermittent peritoneal dialysis (IPD) was performed in 63 (61.2%) and daily hemodialysis (DHD) in 40 (38.8%). IPD was the predominant method during the period from 1985 to 1996 and DHD during the period from 1997 to 2006 (Figure 1). The change in dialytic methods from IPD to DHD was associated with a decrease in mortality ($p < 0.05$). The use of antibiotics was not associated with lower mortality ($p > 0.05$). These data are shown in Table 4.

Death occurred in 31 cases (15.4%). The main cause of death was pulmonary hemorrhage. Mortality rate was higher in the first decade than in the second one, 22.3% vs. 10.3%, respectively ($p = 0.02$). Factors associated with death were oliguria (OR = 7.5, 95% CI = 1.6-47.4), crackles on lung auscultation (OR = 8.01, 95% CI = 1.6-40.1) and advanced age (OR = 1.07, 95% CI = 1.01-1.14).

DISCUSSION

Leptospirosis is the most widespread zoonosis in the world, particularly in warm and humid places as in tropical countries. Most of the cases occur in men.[9,11,15,17] The disease is more common among young people, as confirmed in the present study.[9,11,16,19] The cases described here represent the severe end of the spectrum of leptospirosis. The availability of laboratory diagnostic tests would probably reveal many more cases, most of them anicteric.

The transmission usually results from direct or indirect exposure to the urine of leptospiruric animals. Farming is classically an occupation at increased risk.[5] Mansour-Ghanaei *et al.*[9] found it as the main (60%) occupation among infected patients. Leptospirosis is also related to recreational activities.[4,19]

It is important to identify the serovars associated with human infections by leptospires. Andrade *et al.*[20] identified the serovars *Icterohaemorrhagiae* and *Copenhageni* in 71% and 18% of patients, respectively. Jauréguiberry *et al.*,[19] studying 34 patients, identified the serovars *Grippotyphosa* (30%), *Icterohaemorrhagiae* (15%) and *Copenhageni* (12%). Ko *et al.*[3] found *Leptospira interrogans* serovar *Copenhageni* in 87% of the cases with positive blood cultures of patients with severe leptospirosis. In the present study, microagglutination test was positive in 100% for *Icterohaemorrhagiae* and in 59% for *Copenhageni.*

In the present study, the main clinical signs and symptoms presented by the initial evaluation were fever (96%), jaundice (94%), myalgia (92%), headache (74%) and vomiting (71%). These are the most common findings reported in leptospirosis.[1,7,8,9,17,19]

Hemorrhagic manifestations are characteristic of Weil disease, and are potentially fatal. Patients can develop important hemodynamic abnormalities, secondary to hypovolemia, which is caused by dehydration and direct effects of *Leptospira* toxins that damages vascular endothelium and increases permeability.[21] Hemorrhage has become recognized as the most important manifestation of human leptospirosis and is increasingly reported over the world. Bleeding in leptospirosis may be the result of a defect in the primary hemostasis or a imbalance in secondary hemostasis by depletion of coagulation proteins because of enhanced coagulation or by activated fribrinolysis.[22] In a recent study, Chierakul *et al.* measured plasma concentrations of fibrinogen, D-dimer, thrombin-antithrombin III complexes, and prothrombin fragment 1.2 and evaluated the disseminated intravascular coagulation score. The median concentrations of fibrinogen, D-dimer, thrombin-antithrombin III complexes, and prothrombin fragment 1.2 were significantly elevated in leptospirosis. Patients with leptospirosis had significantly longer prothrombin times, longer activated partial thromboplastin times, and lower platelet counts.[23] In the present study, hemorrhagic manifestations were present in 36% of the patients and the main manifestations were petechias, hemoptysis and hematemesis.

Acute kidney injury in leptospirosis is reported in 40-60% of severe cases[24] and is usually non-oliguric[15,16,25.] Daher *et al.*[15] found a significantly higher mortality in patients with oliguric leptospirosis than in non-oliguric forms. In the present study, oliguria was observed in one third of the patients. Leptospirosis is one of the few causes of AKI that may present with hypokalaemia. Seguro *et al.*[25] found hypokalemia in 45% of 56 patients. In the present study, acute kidney injury was found in 87% of the patients and 63.7% had serum potassium lower than 3.5mEq/L. Daher *et al.*[16] showed that, after leptospirosis AKI, renal function recovery is fast and complete after six months, except for urinary concentration capacity.

Thrombocytopenia is found in 50% of patients with leptospirosis and it correlates with worse prognosis.[26] Tantitanawat & Tanjatham[27] found that platelet count lower than 100,000/mm^3 was an independent risk factor for death in leptospirosis patients. Other reports showed low platelets at admission in almost 95%.[16,28] In the present study, 74% of the patients had platelet count lower than 100,000/mm^3.

In leptospirosis, serum bilirubin can be markedly elevated as compared with other liver enzymes.[1,29] Tantitanawat & Tanjatham[27] found that total bilirubin higher than 2.5 mg/dL was independently associated with severity. In the present study, direct and indirect bilirubin were 13 and 5 mg/dL, respectively, and 85% presented direct bilirubin higher than 3.5 mg/dL.

Chang *et al.*[29] found AST and ALT levels of 117.27 and 70.63 IU/L respectively. Jauréguiberry *et al.*[19] found AST and ALT levels higher than 40 IU/ L in 83 and 86%, respectively. In a study with 72 patients from Turkey with confirmed diagnosis of leptospirosis the mean AST and ALT levels were higher in nonsurvivors than in survivors. ALT levels were within normal limits in 22.2% of cases, between the upper limit of normal and 200 IU in 61.1%, 200-500 IU in 8.3%, 500-1000 IU in 6.9% and over 1000 IU in 1.4%30. In the present study, mean transaminases levels were 2.5-3 times higher than the normal upper limit. The AST and ALT levels were higher than 40 IU/L in 82 and 72% of the patients, respectively. Icteric patients with mild increases in transaminases should always raise the suspicion of leptospirosis.

Urinalysis is frequently abnormal in leptospirosis, with hematuria occurring during the early phase of the illness.[31] Hematuria was reported in 58-70% of patients with leptospirosis.[9,19] In the present study, hematuria was found in 43% of patients.

The true incidence of pulmonary involvement is unclear but may range from 20–70%.[32] Pulmonary hemorrhage seems to be increasing among patients with leptospirosis, as suggested by a study performed in Salvador, Brazil.[33] This study identified [47] (10%) patients with severe pulmonary hemorrhagic syndrome (SPHS) among 474 patients with leptospirosis. Among the 47 SPHS case-patients, 7 (15%) and 20 (42%) had pulmonary hemorrhage and respiratory insufficiency, respectively, at the time of hospitalization. Pulmonary hemorrhage is reported in 40-86% of patients with leptospirosis.[33,34] The syndrome of diffuse alveolar hemorrhage, which is potentially lethal, consists of hemoptysis, bilateral airspace opacification on chest radiograph, and a decreased hematocrit secondary to bleeding from pulmonary microvasculature into the alveolar space.[35] Cardiac involvement is common in any form of leptospirosis.[2] Alterations in the electrocardiographic tracing could be observed in the first 24 hours of hospitalization in approximately 2/3 of the patients with leptospirosis.[36] Meningitis can be a significant feature of leptospirosis, mainly in anicteric form. In a retrospective study of 43 children presenting with leptospirosis 23% had meningitis.[2] Pancreatitis is described as an uncommon complication of leptospirosis, but there are a considerable number of reports in literature.[37-40] In the present study, the complications found were pulmonary bleeding (14%), tract intestinal bleeding (13%), atrial fibrillation (11.4%), pulmonary infection (6.0%), meningitis (1.0%) and pancreatitis (0.5%).

In general, acute kidney injury in leptospirosis is hypercatabolic and requires frequent dialysis. In the present study, during the period of 1985 to 1996 the type of dialysis indicated was intermittent peritoneal dialysis (IPD) but in case of extreme hypercatabolism where the removal of urea was inadequately performed by IPD classic hemodialysis or continuous slow hemodialysis in hemodynamically unstable patients were indicated. During the period of 1997 to 2006 only daily hemodialysis was performed in our patients. Dialysis was required for 51% of the patients. The need of dialysis reported in literature ranges from 6% to 49%.[19,41-43] In the present study, intermittent peritoneal dialysis was performed in 61% and daily hemodialysis in 39% of the patients who underwent in dialytic therapy.

Andrade *et al.*[20] compared the "delayed alternate-day" and the "prompt and daily dialysis" in patients with Weil's disease. There was no difference in terms of the time to recovery of renal function, but the mortality was significant lower in the "prompt and daily dialysis" group (17% vs. 67%, $p = 0.01$). In the present study, the type of dialysis during the period of 1985 to 1995 was intermittent peritoneal dialysis and the mortality was 22%. During the period of 1996 to 2006 the early indication and daily hemodialysis was performed and the mortality decreased to 10% ($p < 0.02$).

The indications for antibiotic therapy in leptospirosis remain controversial. Administration of antibiotics seems to be effective when initiated up to the fourth day after onset of symptoms and several studies have suggested that the use of antibiotic therapy could be beneficial.[44,45] Some reports, however, suggest that penicillin therapy did not provide better clinical outcome in patients with leptospirosis and acute kidney injury, mainly after at least four days of symptomatic disease.[12,46] In the present study, Penicillin G was administered in 131 (65%) of the patients. The majority of these patients, in the last decade, promptly received penicillin as soon as they were admitted in the hospital. In this group of patients we observed a decreased mortality.

The pulmonary complications to leptospirosis are the main cause of death in our country.[10] Previous studies shows that the main cause of mortality was acute renal failure, and this has changed in the last years, with pulmonary hemorrhagic complications becoming the most important cause of death in leptospirosis.[11,33] Death is also attributed to acute kidney injury in a significant number of cases.[11,12] Jauréguiberry *et al.*[19] reported no deaths among 34 patients. Costa *et al.*[11] found 14.2% of death among severe leptospirosis cases. Costa *et al.*[12] reported 9% of nonsurvivors among 253 patients. In the present study, death occurred in 15.4% of cases, and the majority of them were due to pulmonary bleeding. Factors associated with death among our patients were oliguria, crackles on lung auscultation and advanced age.

In summary, leptospirosis is a globally relevant disease with potential fatal outcome. Signs and symptoms suggestive of leptospirosis must be known by any physician in order to institute early adequate treatment to improve outcome. Early indication and daily hemodialysis seems to be beneficial in this group of patients.

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