Intensive Care Med (2007) 33:1959–1966
DOI 10.1007/s00134-007-0776-y

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Leptospirosis in Reunion Island (Indian Ocean): analysis of factors associated with severity in 147 confirmed cases

Received: 17 November 2006
Accepted: 18 June 2007
Published online: 17 July 2007

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Abstract *Objective:* Analysis of risk factors associated with severity in patients with confirmed leptospirosis. *Design and setting:* Retrospective study in 147 leptospirosis-confirmed patients at two tertiary nonteaching hospital in Reunion Island. *Patients:* 138 men and 9 women, aged 36 ± 14 years, 80 in the ICU and 67 in medical wards. *Measurements and results:* We collected demographic, clinical, biological, and radiographic data and performed univariate and multivariate analysis to examine risk factors associated with admission in ICU and mortality. Pulmonary forms were more frequent (85%) than in previous reports, with 85 cases (65.3%) on abnormal chest radiography. Among the 38 patients who underwent bronchoalveolar lavage at admission 31 (81.5%) had alveolar hemorrhage. Independent factors related to ICU admission were: age over 46 years (OR 3.02), creatinine higher than 200 μmol/l (6.69), shock (13.87), and acute respiratory failure (20.69). Mortality was 12.9%. The only factor independently related to mortality was need for mechanical ventilation (OR 20.94). *Icterohemorrhagiae* serogroup was found in 62 cases (42.8%) but was not related to death. *Conclusions:* Pulmonary involvement is a major feature in leptospirosis disease but is not associated with poor outcome. Identification of clinical and laboratory findings on admission may help to better characterize severe cases.

Keywords Leptospirosis · Pulmonary manifestations · Risk factor · Mortality · Intensive care · Alveolar hemorrhage

Introduction

Leptospirosis is a zoonosis caused by the genus *leptospira interrogans* and has a worldwide distribution. Although leptospirosis was initially considered an occupational disease, reports of cases have been increasing with participation in water recreational activities [1, 2]. Leptospirosis has a high prevalence in tropical regions during rainy seasons and following hurricanes and flooding [1]. However, leptospirosis is currently considered a reemerging disease in temperate countries in both rural and urban areas [3]. Leptospirosis is an acute febrile illness with nonspecific clin-

ical signs and symptoms and variable manifestations. Massive pulmonary hemorrhage is recognized as life threatening in the severe form of the disease [4–6]. Pulmonary forms of leptospirosis have been reported in the literature, but the exact incidence remains controversial and the exact impact on patient prognosis as well [1, 7–10]. We report a large retrospective series in laboratory-confirmed leptospirosis and analyze factors associated with severity.

Patients and methods

Data collection

We retrospectively analyzed the cases of 147 patients during the period 1992–2003 (138 men, 9 women; age 36 ± 14 years). The patients had been referred to two tertiary hospitals (CHD Felix Guyon, St. Denis, and GHSR, St. Pierre) in Reunion Island (a French territory in the Indian Ocean) and admitted to the Pulmonary, Nephrology, or Infectious Disease Department. Fifty-five patients were admitted to the intensive care unit (ICU) directly after evaluation in the emergency room and; 20 others were transferred secondarily within 48 h after hospital admission and 5 transferred, depending on disease course and physician judgment.

Demographic and epidemiological data were collected (age, gender, occupation or hobbies, exposure to animals). Clinical data included: fever (temperature 38.5 °C or higher), myalgia, arthralgia, oliguria (urine output 500 ml or less per 24 h), cardiovascular collapse (systolic arterial pressure under 80 mmHg or use of vasoactive drugs for more than 4 h). Pulmonary signs were considered in the case of: presence of dyspnea, cough, chest pain, pulmonary rales at examination, or hemoptysis. Gastrointestinal signs were defined as: presence of jaundice, abdominal pain, nausea, vomiting, diarrhea, occlusion, hepatomegalia, or splenomegalia. The clinical hemorrhagic signs recorded were: epistaxis, hematuria, gastrointestinal hemorrhage, conjunctival bleeding, and intra-abdominal hemorrhage. The usual laboratory values were analyzed at the time of admission. Fibroscopy with a bronchoalveolar lavage (BAL) was performed by chest physicians or trained anesthesiologists in intubated or nonintubated patients when needed: (a) at admission for the investigation of pulmonary involvement pending definite diagnosis (assessment of a suspected pulmonary hemorrhage, investigation of acute respiratory failure, suspicion of opportunistic infection); (b) As a routine procedure on the ICU for the diagnosis of nosocomial pneumonia. Chest radiography at admission was analyzed and classified as normal, interstitial, or alveolar patterns and unilateral or bilateral involvement. All analyzed data were recorded at hospital admission or within the first 24 h after admission.

Definitions

A confirmed case was defined as follows: a clinically compatible illness (fever, jaundice, and renal failure known as Weil's disease or symptoms, suggesting an anicteric form of leptospirosis) with more than one laboratory criterion for confirmation: at least fourfold increase in microscopic agglutination test (MAT) titer between acute phase and convalescent phase serum or a single MAT titer 400 or greater. The definitive infecting serogroup was identified with MAT when there was an at least fourfold increase in MAT titer between initial and follow-up phase serum specimens. In this case the serogroup showing the highest titer was considered to be the presumptive infective serogroup. If there was more than one serogroup with the same titer, the presumptive infecting serogroup was considered as "indeterminate".

Pulmonary involvement was considered positive if the patient (a) presented with a massive alveolar hemorrhage or (b) had at least two clinical signs as previously described (with or without an abnormal chest radiography). Pulmonary hemorrhage was defined when the BAL recovered a bloody liquid with a Golde score higher than 100 or in the case of formal macroscopic bleeding. Nosocomial pneumonia was defined as usual (acquisition of pulmonary infection 72 h after hospital admission and confirmed by a positive BAL with bacterial identification species over 10^4 CFU/ml). Acute respiratory failure was defined according to recommendations [11]. The biological variables were set at a relevant cutoff point demonstrating significant organ dysfunction. The following criteria were used: white blood cell count higher than 13,000 m/l, platelet count less than 50,000 m/l, hemoglobin below 8 10^9/dl, prothrombin ratio lower than 50%, total bilirubin higher than 200 μmol/l, aspartate aminotransferase higher than 150 UI/l, alanine aminotransferase higher than 150 UI/l, serum creatinine kinase above 2,500 UI/l, blood urea nitrogen above 15 mmol/l, serum creatinine higher than 200 μmol/l, kaliemia greater than 5 mmol/l, arterial pH less than 7.35, total serum CO_2 below 18 mmol/l, arterial oxygen tension below 60 mmHg, and arterial carbon dioxide tension above 45 mmHg. Regarding biological parameters, only initial values were used.

Statistical analysis

Signs and symptoms of disease are reported as mean ± standard deviation or percentages. The Mann–Whitney *U*-test was used to assess differences in continuous variables. Clinical factors, therapeutic issues, and laboratory findings were analyzed in patients admitted to the ICU vs. those admitted to medical wards and in survivors vs. nonsurvivors by univariate analysis using the χ^2 or Fisher's exact test. Variables with a *p*-value less

than 0.20 in the univariate analysis with less than 5% missing data were entered in a backward multiple logistic regression. Variables with $p < 0.05$ were selected in the final model. Adjusted odds ratio (OR) and 95% confidence intervals (CI) were calculated. Analyses were performed with the SAS system version 8.

Results

A risk factor (RF) for leptospirosis disease was recorded in 71 patients (48.2%), principally a occupational RF (35.5% of farmers). Signs and symptoms of disease are presented in the Table 1. We found few underlying diseases in this young population (only six patients were aged over 60 years; 60 ± 4.4). Two patients had alcoholic liver cirrhosis, one underwent splenectomy, one had a mild renal insufficiency due to anatomical malformation, 12 (8%) had diabetes with no insulin supplementation, 4 (2.7%) had chronic obstructive lung diseases, and 3 (2%) had blood hypertension. Pulmonary involvement was found in 85% of patients. Among the 38 patients who underwent BAL at admission 31 (81.5%) had an alveolar hemorrhage. In these 31 patients 12 (38.7%) had normal radiography. Chest radiography was abnormal in 65.3% of the analyzed patients (85/130). All but two patients had bilateral involvement on chest radiography; 56 had interstitial features and 29 alveolar patterns.

Outcome was not significantly affected by the administration of antibiotics (penicillin G, $n = 79$; penicillin A, $n = 34$; third-generation intravenous cephalosporin, $n = 19$; erythromycin, $n = 4$; total $n = 136$, 92.5%). Biological results are listed in the Table 2. Admission to the ICU was frequent and reflects severe forms of the disease, as indicated by the rate of shock (12.9%) and death (12.9%). A definite serogroup was obtained in 89 patients (60.5%), *Icterohemorrhagiae* was the most frequent (42.8%). Table 3 presents the univariate analysis results of the clinical factors, therapeutic issues, and laboratory findings for ICU vs. non-ICU patients. Results of the multivariate analysis are presented in Table 4; factors independently related to severity were:

Table 1 Clinical findings for 147 cases of confirmed leptospirosis (*COPD*, chronic obstructive pulmonary disease; *SAPS*, Simplified Acute Physiology Score)

Sign and symptoms	Mean ± SD or *n* (%)	Number of patients with data available
Risk factors for leptospirosis	71 (48.2%)	147
Occupation	50 (35.5%)	
Rodents bite	5 (3.5%)	
Recreational	16 (11.3%)	
Comorbidities		147
Age > 60 years	6 (4%)	
Diabetes	12 (8%)	
COPD	4 (2.8%)	
Blood hypertension	3 (2%)	
Liver cirrhosis	2 (1.3%)	
Fever	119 (85%)	140
Myalgia	104 (74%)	140
Headache	60 (41.9%)	143
Arthralgia	35 (28.4%)	123
Jaundice	110 (77.5%)	142
Diarrhea	13 (9.1%)	125
Abdominal pain	58 (43.6%)	133
Vomiting	54 (39.8%)	133
Hepatomegaly	22 (18.3%)	120
Splenomegaly	6 (5%)	120
Oliguria or anuria	49 (34.5%)	142
Pulmonary involvement	125 (85%)	147
Dyspnea	51 (34.9%)	146
Thoracic pain	17 (11.5%)	147
Cough	68 (46.2%)	147
Hemoptysis	51 (35.9%)	142
Pulmonary rales	50 (34.9%)	143
Alveolar hemorrhage	31 (81.5%)	38
Abnormal chest radiography	85 (65.3%)	130
Interstitial	56 (66%)	
Alveolar	29 (34%)	
Bilateral	83 (97.6%)	
Admission in ICU	80 (54.5%)	147
Mean SAPS score (for ICU only)	28 ± 14	80
Shock	19 (12.9%)	147
Mortality	19 (12.9%)	147

Table 2 Laboratory and bacteriological findings

	Mean ± SD or *n* (%)	Number of patients with data available
Blood urea nitrogen (mg/dl)	19.7 ± 12	141
Creatinine (μmol/l)	420 ± 287	147
Creatinine kinase (UI/l)	2529 ± 5,947	110
Aspartate transaminase (UI/l)	143 ± 173	143
Alanine transaminase (UI/l)	85 ± 110	129
Total bilirubine level (mg/dl)	213 ± 191	144
Lactico dehydrogenase (UI/l)	805 ± 645	77
White blood cell count	12,832 ± 5,265	143
Platelets count	84,375 ± 57,669	144
Hemoglobin (10^9/l)	12.2 ± 2.2	143
Prothrombin ratio (%)	89 ± 14.5	138
Fribrinogen (g/l)	7.4 ± 2.29	101
Cephaline caoline time	34 ± 6.8	132
PaO_2 (mmHg)	79.3 ± 28	101
$PaCO_2$ (mmHg)	34.1 ± 6.5	101
Total serum CO_2	23.69 ± 4.56	101
Definite serogroups	89 (60.5%)	147
Icterohemorrhagiae	63 (42.8%)	
Woolfi	7 (4.7%)	
Serojae	7 (4.7%)	
Canicola	7 (4.7%)	
Miscellaneous	5 (3.4%)	
Indeterminate	58 (39.4%)	

Table 3 Univariate analysis for clinical and laboratory findings for ICU vs. medical ward patients (*CI*, confidence interval; *ARF*, acute respiratory failure; *MV*, mechanical ventilation; *WBC*, white blood cells; *ASAT*, aspartate transaminase; *ALAT*, alanine transaminase; *CPK*, creatinine kinase; *BUN*, blood urea nitrogen; *CO_2T*, total serum CO_2; *PaO_2*, arterial oxygen tension; *$PaCO_2$*, arterial carbon dioxyde tension)

	ICU patients ($n = 80$)	Non-ICU patients ($n = 67$)	Odds ratio	95% CI	*p*
Age > 46 years	25/80 (31.3%)	10/67 (15%)	2.59	1.1–5.9	0.02
Oligoanuria	35/79 (44.3%)	14/63 (22%)	2.78	1.4–5.8	0.006
Shock	18/80 (22.5%)	1/67 (1.5%)	19.16	2.5–147.8	0.0002
Pulmonary involvement	68/79 (86.1%)	57/67 (85%)	1.08	0.4–2.7	0.86
Alveolar hemorrhage	21/24 (60%)	10/14 (80%)	2.8	0.05–15	0.38
ARF	41/80 (51.3%)	3/67 (4.5%)	22.4	6.5–77.3	0.0001
MV requirement	25/80 (31.5%)	0 (0%)	85	5.1–1439	0.0001
Dialysis requirement	36/80 (28.8%)	9/65 (13.9%)	5.09	2.2–11.6	0.0001
WBC > 13,000	39/77 (50.7%)	19/66 (28.8%)	2.53	1.2–5.08	0.007
Platelets < 50,000	29/79 (36.7%)	11/65 (16.9%)	2.84	1.3–6.3	0.008
Hemoglobin < 8 10^9/dl	5/76 (6.6%)	0 (0%)	10	0.5–190	0.06
Prothrombin ratio < 50%	2/78 (2.6%)	0 (0%)	4.4	0.2–96	0.5
Total bilirubin > 200 μmol/l	41/79 (51.9%)	18/65 (27.7%)	2.81	1.4–5.7	0.003
ASAT > 150 UI/l	24/78 (30.8%)	12/65 (18.5%)	1.96	0.9–4.3	0.09
ALAT > 150 UI/l	11/67 (16.4%)	3/62 (4.8%)	3.86	1–14.5	0.03
CPK > 2500 UI/l	19/61 (31.1%)	11/49 (22.5%)	1.56	0.7–3.7	0.3
LDH > 700 UI/l	23/41 (56.1%)	7/36 (19.4%)	5.29	1.9–14.8	0.001
BUN > 15 mmol/l	57/79 (72.2%)	21/62 (33.9%)	5.05	2.5–10.4	0.0001
Creatinine > 200 μmol/l	67/80 (83.8%)	29/67 (43.3%)	6.7	3.1–14.5	0.0001
Kaliemia > 5 mmol/l	10/80 (12.5%)	6/67 (9%)	1.45	0.5–4.2	0.49
pH < 7.35	9/71 (12.7%)	0 (0%)	8.6	0.5–154	0.06
CO_2T < 18 mmol/l	7/69 (10.1%)	1/31 (3.2%)	3.38	0.4–28.7	0.42
PaO_2 < 60 mmHg[a]	20/71 (28.2%)	5/29 (17.2%)	1.88	0.6–5.6	0.25
$PaCO_2$ > 45 mmHg	5/71 (7%)	0 (0%)	5	0.2–94	0.31
Mortality	16/80 (20%)	3/67 (4.4%)	5.33	1.5–19.2	0.006

[a] At room air or with oxygen (for some patients initial measurement was performed with oxygen supplementation at admission)

Table 4 Multivariate analysis for risk factors related to admission in ICU (the variable mechanical ventilation requirement was not included in the logistic regression model)

	Odds ratio	95% CI	*p*
Age > 46 years	3.02	1.1–8.4	0.03
Creatinine > 200 μmol/l	6.69	2.6–17.6	0.0001
Shock	13.87	1.5–132.8	0.02
Acute respiratory failure	20.69	5.3–80.5	0.0001

Table 5 Univariate analysis for clinical factors, therapeutic issues and laboratory findings in survivors and nonsurvivors patients (*CI*, confidence interval; *ARF*, acute respiratory failure; *AB*, antibiotics; *WBC*, white blood cells; *ASAT*, aspartate transaminase; *ALAT*, alanine transaminase; *CPK*, creatinine kinase; *PT*, prothrombin; *BUN*, blood urea nitrogen; CO_2T, total serum CO_2)

	Non-survivors ($n = 19$)	Survivors ($n = 128$)	Odds ratio	95% CI	*p*
Age > 46 years	7/19 (36.8%)	28/128 (21.9%)	2.08	0.7–5.8	0.15
ICU admission	16/19 (84.2%)	64/128 (50%)	5.33	1.5–19.2	0.005
Shock	6/19 (31.6%)	13/128 (10.2%)	4.08	1.3–12.5	0.019
Oligoanuria	10/18 (55.6%)	39/124 (31.5%)	2.72	1–7.4	0.04
Dialysis requirement	9/19 (47.4%)	36/126 (28.6%)	2.25	0.8–6	0.09
Pulmonary involvement	17/19 (89.5%)	108/127 (85%)	1.49	0.3–7	1
Alveolar hemorrhage	3/19 (16%)	28/128 (22%)	0.66	0.2–2.5	0.7
ARF	14/19 (73.7%)	30/128 (23.4%)	9.14	3–27.5	0.0001
MV requirement	13/19 (68.4%)	12/128 (12/128%)	20.9	6.7–65	0.0001
Nosocomial VAP	11/19 (58%)	12/128 (9%)	13.29	4.5–39.4	0.0001
AB administration	19/19 (100%)	11/128 (86%)	3.8	0.2–67	0.35
WBC > 13,000	11/19 (57.9%)	47/124 (37.9%)	2.25	0.8–6	0.09
Platelets < 50,000	9/19 (47.4%)	31/125 (25%)	2.72	1–7.3	0.04
Hemoglobin < 8 10^9/dl	2/19 (10.5%)	3/124 (2.4%)	4.74	0.7–30.5	0.13
PT ratio < 50%	2/19 (10.5%)	0/119	1.11	0.9–1.3	0.02
Total bilirubin > 200 μmol/l	10/19 (52.6%)	49/125 (39%)	1.72	0.7–4.6	0.31
ASAT > 150 UI/l	7/19 (36.8%)	29/124 (23.4%)	1.91	0.7–5.3	0.26
ALAT > 150 UI/l	2/14 (14.3%)	12/115 (10.4%)	1.43	0.3–7.2	0.65
LDH > 700 UI/l	8/11 (72.7%)	22/66 (33.3%)	5.33	1.3–22.1	0.019
CPK > 2500 UI/l	6/15 (40%)	24/95 (25%)	1.97	0.6–6.1	0.34
BUN > 15 mmol/l	17/19 (89.4%)	60/123 (47%)	4.76	1.2–17.3	0.01
Creatinine > 200 μmol/l	16/19 (84.2%)	80/128 (62.5%)	3.2	0.9–11.6	0.06
Kaliemia > 5 mmol/l	3/19 (15.8%)	13/128 (10.2%)	1.65	0.4–6.5	0.43
pH < 7.35	1/18 (5.6%)	8/81 (9.9%)	0.5	0.06–4.6	1
CO_2T < 18 mmol/l	4/18 (22.2%)	4/82 (4.9%)	5.57	1.2–25	0.03
Icterohemorrhagiae serogroup	7 (36.8%)	56 (43.7%)	0.82	0.3–2.3	0.8

age over 46 years (OR, 3.02, 95% CI 1.1–8.4, $p < 0.05$), creatinine higher than 200 μmol/l (OR 6.69, CI 2.6–17.6, $p < 0.001$), shock (OR 13.87, CI 1.5–132.8, $p < 0.05$), and acute respiratory failure (OR 20.69, CI 5.3–80.5, $p < 0.0001$). Variables related to death on univariate analysis are presented in Table 5. Multivariate analysis found that requirement of mechanical ventilation (MV) was the only independent factor related to mortality (OR 20.94, CI 6.7–65.2, $p < 0.0001$). Duration of MV was longer in survivors (7 ± 8.2 days) than in nonsurvivors (4 ± 4.7 days, $p < 0.007$).

Discussion

This study produced two important findings: a higher rate of pulmonary forms (85%) than has generally been reported in the literature and a high ICU admission rate (54.5%). Mild pulmonary involvement has been reported in 20–70% of leptospirosis patients but is often overshadowed by other manifestations [8, 12]. Pulmonary manifestations are considered uncommon in Europe [13] but more frequent in tropical areas [1, 2, 9, 14, 15]. Predominant pulmonary presentation has been reported in patients with little or no jaundice [16]. However, we found a high rate of pulmonary involvement in our patients who also had an icteric form of leptospirosis (77.5%), but with no relationship to poor outcome.

Abnormalities on chest radiography may be underdiagnosed by nonskilled physicians. Some slight features may be not recognized as pathological or be attributed to oliguria or others underlying conditions. This is important for the analysis of interstitial features on chest radiography. Pulmonary manifestations are generally recorded in the case of severe illness such as massive pulmonary hemorrhage [5, 6, 17, 18]. We observed massive hemoptysis at admission in only three patients, two of whom died. Pulmonary hemorrhage can also be occult with few or no chest radiography abnormalities despite presence of clinical symptoms (cough, abnormal chest auscultation) [19].

Among the 31 patients with alveolar hemorrhage confirmed by BAL 12 (38.7%) had normal chest radiography. In these conditions high-resolution computed tomography may reveal ground glass opacification consistent with the diagnosis of alveolar hemorrhage [20]. In our opinion, alveolar hemorrhage may be constant in leptospirosis and reflects pulmonary tissue injury. The pathophysiology of tissue damage in leptospirosis is still uncertain. Intact leptospira have been found in kidney, intestine, spleen, and lungs in animal models [21]. These data were confirmed in humans in a leptospirosis outbreak in Nicaragua and recently in India [8, 18, 22]. The number of leptospira is variable and depends on the organs; it is high in kidney but rare in the lungs. However, tissue damage is important in all involved organs and can reach 70% of the total lung parenchyma in infected guinea pigs, suggesting immunological disorders [18, 21]. Use of corticosteroids in this indication may be beneficial [23, 24].

Our high ICU rate admission reflected the severity of the disease. Of the 80 patients referred to the ICU in this study 75 (55 immediately) were admitted within the first 48 h after hospital presentation. The multivariate analysis found four variables related to ICU admission. Shock was a major issue and reflected more extreme severe disease with multiple organ failure than a specific myocarditis involvement due to leptospirosis [25, 26]. Patients with acute respiratory failure needed intensive care, and this was not surprising. We did not include in the multivariate analysis model the variable of requiring MV as all the patients who needed MV were automatically referred to ICU. Acute renal failure with creatinine level over 200 μmol/l was correlated to ICU admission.

To date there are no specific guidelines for the management of acute renal failure due to leptospirosis. In our study the majority of nonoliguric cases had a spontaneous recovery, as did some patients with severe acute renal failure without dialysis [27]. There are few reports in the literature on the use of dialysis in leptospirosis (except in life-threatening conditions). Recently Vickery et al. [28] reported favorable outcome in a small series of 15 patients with acute renal failure. They used continuous venovenous hemofiltration at 1000 ml/h filtration and 1000 ml dialysis. This technique is certainly safer than conventional dialysis which requires more anticoagulant agents. In our study ICU patients received preferentially continuous venovenous hemofiltration, and medical ward patients only conventional dialysis. In these conditions it is difficult to compare the results and to assess a favorable or unfavorable issue. Recommendations will be mandatory for the use of dialysis in leptospirosis as acute renal failure was correlated to mortality in former reports [26, 29]. The last variable correlated to severity was uncommon: age over 46 years. However, the study population was young and active with few comorbidities. In these severe patients it is possible that tolerance of the disease was higher in young adults than in middle-aged patients.

Another important issue is the mortality analysis. We observed a high mortality rate (12.9%). The proportion of deaths in previous reports has been about 5% [16, 30–32]. However, mortality was higher in some studies, as reported in the French West Indies (18%) [26], Thailand (14%) [33], and Brazil (15%) [34]. Our univariate analysis showed the usual variables generally correlated to a poor outcome, except that requirement of MV was an independent factor for mortality. However, the indication and duration of MV was not identical in all deceased patients. However, long duration of MV was associated with better prognosis. These results may indicate that the most patients with the most severe condition rapidly died of multiple organ failure, and that this can be attributed to leptospirosis. Others MV patients may improve with MV discharge before they acquire a nosocomial pneumonia (ventilated acquired pneumonia). For thos acquiring ventilator-associated pneumonia in this way the prognosis was poor and was related of the general prognosis of ventilator-associated pneumonia regardless of the reason for ICU admission. Deaths direct attributable to leptospirosis were easy to determine in patients with rapidly fatal outcome. These patients had a dramatic course with multiple organ failure or predominant acute respiratory distress syndrome related to massive intra-abdominal hemorrhage. Death occurred generally within the first week. It was more confusing when features of leptospirosis disease were still present, and when ICU complications occurred. In the patients who died later mortality was related more to complications of ICU procedure than to leptospirosis. In the three patients who died in medical wards one did so during dialysis with hemorrhage (not related to leptospirosis patterns); for the two others no definite cause was recorded.

In summary, some clinical and laboratory criteria must be considered as indicating risk, and some patients must be considered for ICU referral. Pulmonary forms were common but did not have a poor prognosis. Additional studies are warranted to better characterize severe patients and to precise therapeutic procedures in the ICU [35]. For the most severe patients with rapid course to multiple organ failure leptospirosis remains a major medical challenge.

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