

RISK FACTORS FOR DEATH AND CHANGING PATTERNS IN LEPTOSPIROSIS ACUTE RENAL FAILURE

ELIZABETH DAHER, DIRCE M. TREVISAN ZANETTA, MARCELO BORGES CAVALCANTE, AND REGINA C. R. M. ABDULKADER

Departamento de Medicina Clínica, Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza, Brazil;
Departamento de Epidemiologia e Saúde Coletiva, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, Brazil;
Disciplina de Informática Médica, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil;
Grupo de Insuficiência Renal Aguda, Hospital das Clínicas, Disciplina de Nefrologia, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil

Abstract. The risk factors for death and changes in clinical patterns in leptospirosis (Weil's disease) have not been well studied. We retrospectively studied 110 patients with Weil's disease hospitalized in Brazil between 1985 and 1996. Univariate statistical analysis showed that nonsurvivors were older than survivors, and had higher frequency of oliguria, cardiac arrhythmia, dyspnea, and pulmonary rales. Logistic regression showed that the only independent factor associated with death was oliguria (odds ratio [OR] = 8.98). The presence of arthralgia (OR = 4.71), dehydration (OR = 6.26), dyspnea (OR = 17.7), and pulmonary rales (OR = 9.91) increased after 1994. These data suggest that in Weil's disease the clinical patterns have changed and the presence of oliguria is a risk factor for death.

Risk factors for death in acute renal failure due to acute tubular necrosis have been intensively investigated, but only a few studies have considered these risks when acute renal failure is due to leptospirosis (Weil's disease).^{1,2} Acute renal failure due to leptospirosis can be distinguished from acute tubular necrosis because it usually occurs in previously healthy young males and has a high prevalence of hypokalemic and nonoliguric forms.^{3,4}

The reported mortality due to leptospirosis varies from 19% in Barbados,⁵ 10% in Hawaii,⁶ 8% in Trinidad,⁷ and 5% in Korea.⁸ In the absence of acute renal failure, death due to leptospirosis is very uncommon, but the reported mortality due to leptospirosis with acute renal failure is high: 36% in Barbados,⁹ 26% in Sri Lanka,¹⁰ and 17% in Turkey.¹¹ Some factors seem to be related to death in Weil's disease such as age, gender, presence of oliguria, jaundice, and pulmonary involvement.^{3,5,8,10,12,13}

In a hospital in Sao Paulo, Brazil, the Instituto de Infecç ologia Em lio Ribas, the mortality rate was 18% among adult patients admitted in the 1980s with severe Weil's disease and 2% among children admitted in the 1990s.^{3,14} Everard and others showed a trend for the mortality that increased with age.⁵ On the other hand, Dupont and others did not find age to be an independent factor associated with mortality.¹²

There is some evidence that females, although having leptospirosis less frequently, could have a higher mortality rate. Everard and others showed that females, who represented only 25% of the studied patients, had a mortality rate twice as high as males.¹³

Seguro and others reported a 50% mortality rate among oliguric patients with Weil's disease and 5% among nonoliguric patients.³ Dupont and others also found oliguria to be an independent factor associated with mortality in hospitalized patients with leptospirosis.¹² Ramachandran and others found bilirubin levels of approximately 15 mg/dL among the leptospirosis oliguric patients who died and 5 mg/dL among the oliguric or nonoliguric survivors.¹⁰ Dupont and others studied hospitalized patients with leptospirosis and found either dyspnea or alveolar infiltration to be independent factors associated with mortality.¹² At the Instituto de Infecç ologia

Em lio Ribas, the mortality rate was 18% among leptospirosis patients with acute renal failure and 54% among those with leptospirosis, acute renal failure, and pulmonary hemorrhage (Marotto PCF, unpublished data).³

In the last five years in Brazil, we have observed what might be a change in the clinical characteristics of hospitalized leptospirosis patients: more severe cases have been detected mainly with pulmonary involvement. Also, in the last 3 years, 2 outbreaks of leptospirosis with pulmonary involvement were reported in India and Nicaragua.^{15,16} To test this possibility, we analyzed the frequency of each symptom or clinical sign in patients from 1985 to 1996. The objectives of this study were to address the following questions about hospitalized patients with leptospirosis and acute renal failure: 1) What are the risk factors for death? And 2) Have the clinical characteristics of patients changed in the last five years?

PATIENTS AND METHODS

The study was performed at the University Hospital Walter Cant dio, in Fortaleza, Cear  State, in northeastern Brazil. This hospital serves the city of Fortaleza and its surroundings. In this region, approximately 50 cases of leptospirosis per year have been reported since 1985. The records of all 110 patients hospitalized from May 1985 to September 1996 with a diagnosis of leptospirosis and acute renal failure were retrospectively evaluated. To ensure that only cases of clinically significant acute renal failure were evaluated, the adopted criterion for acute renal failure was the occurrence of at least one plasma creatinine (P_{creat}) value $\geq 177 \mu\text{mol/L}$ during hospitalization (normal values = 50–110 $\mu\text{mol/L}$). Symptoms and signs identified during a physical examination at hospital admission were analyzed. The systolic and diastolic blood pressures (BP_s and BP_d) and laboratory parameters at hospital admission were also evaluated. Laboratory parameters included plasma sodium and potassium (P_{Na} and P_{K}), blood urea nitrogen (BUN), P_{creat} , number of leukocytes and platelets, hemoglobin, aspartate and alanine aminotransferases (AST and ALT), and conjugated and unconjugated bilirubins (CB and UB). Minimum levels of P_{Na}

and P_K throughout hospitalization and maximum levels of BUN and P_{creat} were also recorded. Mean arterial blood pressure was calculated for each patient by the formula $BP_m = (BP_s + 2BP_d)/3$. Total bilirubin (TB) was calculated for each patient by adding the CB and UB values. Other variables analyzed were the presence of oliguria (urinary volume < 600 ml/day after hydration), the need for dialysis, the number of dialysis procedures performed, time (in days) between admission and death or discharge, and the use of penicillin as a specific treatment. When administered, the dosage of penicillin was 8 million units/day given intravenously for 7 days. When dialysis was necessary, peritoneal dialysis was done.

The study was approved by the Ethics Committee of the University Hospital Walter Cantúdio. The Ethics Committee indicated that informed consent was not necessary because the study was retrospective, based only on chart review, with no individual identification of patients.

Statistical analysis. Statistical analysis consisted of univariate and bivariate analysis of clinical and laboratory data with the Student's *t*-test or analysis of variance, the Mann-Whitney test or Kruskal-Wallis test as appropriate for quantitative variables, and the chi-square test with Yates' correction or Fischer's exact test for comparisons of proportions and qualitative variables (Epi-Info software; Centers for Disease Control and Prevention, Atlanta, GA). A logistic regression model (BMDP Statistical Software, Inc., Los Angeles, CA) analysis was performed to determine those factors significantly associated with death while simultaneously accounting for potentially confounding factors. The original model related survival status with biologic and clinical known risks of death and those variables that were significant in the bivariate analysis. Continuous variables were categorized for the analysis using their mean as the cut-off point. The significance of each variable in the model was evaluated by the Wald test. Logistic regression, controlling for potentially confounding factors, was also used to evaluate the patterns of leptospirosis clinical presentation over time, testing if the prevalence of each sign and symptom had changed. Adjusted odds ratio (ORs) and 95% confidence intervals (CIs) were calculated. Data are presented as mean \pm SD or a percentage. The significance level used was $P \leq 0.05$.

RESULTS

Eighty six patients were males and 24 were females. Their ages ranged from 8 to 84 years (mean \pm SD = 41 ± 18 years). The mean \pm SD age was 42 ± 18 years for males and 43 ± 18 years for females ($P = 0.76$). Overall mortality was 22% (24 patients). Nonsurvivors were older than survivors (52 ± 19 versus 38 ± 17 years; $P = 0.001$). Sixteen percent of the males died compared with 35% of the females ($P = 0.07$). Older age was associated with death in the male group (55 ± 19 years for nonsurvivors versus 38 ± 16 years for survivors; $P = 0.001$), while this difference was not observed in the female group (nonsurvivor females = 49 ± 17 years and survivor females = 40 ± 17 years; $P = 0.20$). The frequency of some of the symptoms and physical findings at hospital admission is presented in Table 1.

The initial P_{Na} was 134 ± 7 mmol/L ($n = 107$) and the

TABLE 1
Frequency of symptoms and physical findings in survivors and nonsurvivors with leptospirosis*

	Nonsurvivors	Survivors	P
Fever	100% (n = 22)	97% (n = 87)	NS
Headache	50% (n = 22)	74% (n = 85)	NS
Myalgia	82% (n = 22)	95% (n = 86)	0.05
Dehydration	57% (n = 21)	69% (n = 87)	NS
Jaundice	100% (n = 22)	98% (n = 87)	NS
Cardiac arrhythmia	36% (n = 22)	13% (n = 86)	0.02
Pulmonary rales	32% (n = 22)	12% (n = 86)	0.04
BPs (mm of Hg)	104 ± 17 (n = 20)	110 ± 18 (n = 83)	NS
BPd (mm of Hg)	60 ± 11 (n = 20)	68 ± 15 (n = 83)	0.02

* NS = not significant; BPs = systolic blood pressure; BPd = diastolic blood pressure.

minimum P_{Na} was 133 ± 7 mmol/L ($n = 106$). The initial P_K was 4.0 ± 1.0 mmol/L ($n = 108$) and the minimum P_K was 3.2 ± 0.6 mmol/L ($n = 107$). Initial and maximum values for BUN and P_{creat} were 32.5 ± 15.0 mmol/L ($n = 110$) and 36.1 ± 15.0 mmol/L ($n = 110$) and 539 ± 248 $\mu\text{mol/L}$ ($n = 110$) and 601 ± 256 $\mu\text{mol/L}$ ($n = 110$), respectively. Only minimum P_K values showed a significant difference ($P = 0.01$) between survivors (3.2 ± 0.5 mmol/L, $n = 87$) and nonsurvivors (3.6 ± 0.8 mmol/L, $n = 20$). At admission, blood pH and plasma bicarbonate were recorded in 59 patients and nonsurvivors had lower values of both variables than the survivors: pH = 7.33 ± 0.15 , $n = 17$ versus 7.39 ± 0.07 , $n = 42$; $P = 0.10$; plasma bicarbonate = 18 ± 6 mmol/L, $n = 17$ versus 22 ± 5 mmol/L, $n = 42$; $P = 0.02$. These data suggest that metabolic acidosis predominated in the nonsurvivors and consequently they showed higher P_K values.

Hematologic parameters showed the following values: hemoglobin = 104 ± 20 g/L ($n = 107$), hematocrit = 0.33 ± 0.06 ($n = 109$), leukocytes = 14.4 ± 6.5 $10^9/\text{L}$ ($n = 95$), and platelets = 68 ± 57 $10^9/\text{L}$ ($n = 80$). Hepatic evaluation showed the following values: AST = 1.32 ± 0.95 $\mu\text{kat/L}$ ($n = 90$), ALT = 1.02 ± 1.18 $\mu\text{kat/L}$ ($n = 90$), CB = 257 ± 171 $\mu\text{mol/L}$ ($n = 90$), and UB = 103 ± 86 $\mu\text{mol/L}$ ($n = 90$). No differences in these hematologic and hepatic variables were found between survivors and nonsurvivors.

The observed prevalence of oliguria was 24% ($n = 104$). Eighty-one percent of the patients ($n = 110$) required dialysis and the mean \pm SD number of dialysis procedures performed among them was 3.1 ± 2.7 ($n = 89$). The prevalence of oliguria was higher among nonsurvivors (56%, $n = 18$) than among survivors (18%, $n = 85$; $P = 0.002$). The prevalence of oliguria was 19% ($n = 86$) among males and 38% among females ($n = 24$; $P = 0.06$).

Penicillin was administered to 36% of the patients. Twenty-six percent of the nonsurvivors and 39% of the survivors were treated. This difference was not statistically significant ($P = 0.46$). The hospitalization period was longer among survivors (15 ± 8 days) than among nonsurvivors (7 ± 8 days; $P < 0.001$), indicating that death usually occurred early during the hospitalization.

The risk factors for death were evaluated by logistic regression. The initial model tested included the following var-

TABLE 2

Final model for the evaluation of risk factors for death due to leptospirosis*

	OR	95% CI	P
Oliguria	8.98	1.81–44.6	0.006
Age	1.55	0.30–7.92	0.59
Cardiac arrhythmia	3.50	0.48–25.3	0.21
Pulmonary rales	2.21	0.43–11.4	0.34
Mean arterial blood pressure	0.28	0.06–1.23	0.09

* OR = adjusted odds ratio; CI = confidence interval.

ables: age ($>$ or \leq 40 years), gender, presence of cardiac arrhythmia, pulmonary rales and of oliguria, mean arterial blood pressure ($BP_m <$ or \geq 70 mmHg), minimum $P_k (<$ or \geq 3.0 mmol/L), level of total bilirubin ($TB <$ or \geq 342 μ mol/L), need for dialysis and maximum BUN ($>$ or \leq 33 mmol/L). The results of the final model are shown in Table 2. The only independent risk factor for death was the presence of oliguria.

To evaluate whether the clinical characteristics of the patients have been changing in the last five years, the frequency of each sign and symptom was verified for the years 1985 to 1990, 1991 to 1993, 1994, and 1995 to 1996. The year 1994 was isolated because an outbreak occurred in that year. Since no differences were found between the 1985–1990 and 1991–1993 periods, they were grouped. The presence of arthralgia, dyspnea, dehydration, peak plasma creatinine $>$ 530 μ mol/L, pulmonary rales, and mortality showed a statistically significant difference among the periods in the bivariate analysis. These data are shown in Table 3.

The relationship of each sign or symptom with time, categorized as above, was evaluated by logistic regression controlling for age and gender. All of the following comparisons used the 1985–1993 period as a reference point. In the 1995–1996 period, the frequency of arthralgia (OR = 4.71, 95% CI = 1.30–17.1, $P = 0.017$), dyspnea (OR = 17.7, 95% CI = 3.1–101, $P < 0.0001$), and dehydration (OR = 6.26, 95% CI = 1.31–29.9, $P = 0.02$) was higher than in the reference period. In 1994, the presence of pulmonary rales increased (OR = 9.91, 95% CI = 2.67–36.8, $P < 0.0001$) and a peak plasma creatinine level greater than 530 μ mol/L was less frequent when compared with the reference period (1985–1993) (OR = 9.40, 95% CI = 2.75–32.1, $P < 0.0001$). The mortality rate when controlled for age and gender showed no difference over time. The frequency of treatment was lower ($P = 0.02$) in 1994 (12%) when compared with the reference period (1985–1993) (38%), and to the period 1995–1996 (56%).

DISCUSSION

The more frequent general symptoms found in this study were fever (97%), headache (69%) and myalgia (93%), as also reported in Puerto Rico, New Caledonia, the United States, Portugal, Hawaii, Korea, and Barbados.^{6,8,17–22} Jaundice was recorded in 98% of the patients, although all had abnormal levels of bilirubins. This percentage was similar to the 85% found in hospitalized patients in French West Indies, 100% in Turkey, 95% in Barbados, and 70% in São Paulo, Brazil.^{11,12,14, 22} However, this frequency was higher

TABLE 3

Frequency of signs and symptoms from 1985 to 1996 in patients with leptospirosis

	1985–1993	1994	1995–1996
Arthralgia	11%	30%	35%
$P = 0.014$	n = 65	n = 20	n = 20
Dyspnea	3%	5%	32%
$P = 0.0001$	n = 67	n = 19	n = 19
Dehydration	58%	80%	81%
$P = 0.02$	n = 66	n = 20	n = 21
Pulmonary rales	6%	40%	24%
$P = 0.001$	n = 66	n = 20	n = 21
Cardiac arrhythmia	12%	29%	24%
$P = 0.45$	n = 66	n = 21	n = 21
Plasma creatinine $>$ 530 μ mol/L	71%	24%	57%
$P = 0.002$	n = 68	n = 21	n = 21
Oliguria	27%	20%	17%
$P = 0.45$	n = 62	n = 20	n = 18
Mortality	19%	38%	5%
$P = 0.042$	n = 67	n = 21	n = 19

than the value of 35% found in hospitalized patients in New Caledonia, 16% in an outbreak in Korea, and 20% among the cases observed in an active surveillance in Hawaii.^{6,8,18} These differences could be explained by the design of each study: hospitalized versus nonhospitalized patients, with or without acute renal failure, the presence or absence of an outbreak.

Clinical symptoms of cardiac involvement have only been occasionally reported: 20% in New Caledonia,¹⁹ 9% in the United States,²⁰ and 18% in Barbados.²² In the present study, the frequency of cardiac arrhythmia at the initial physical examination was 17%, similar to that found in Barbados.²² If the cardiac alterations are detected by electrocardiogram (ECG), the frequency reaches up to 70% as reported for hospitalized patients in India.²³

The reported frequency of pulmonary abnormalities was 27% in the United States in the period 1949–1961, 36% in Puerto Rico in 1963, and 50% in hospitalized patients in 1989 in New Caledonia.^{17,19,20} The frequency of hemoptysis was 7% in 1989 in New Caledonia, 40% in an outbreak in 1987 in Korea, and 49% in an outbreak in India in 1993.^{8,15,19} However, occult alveolar hemorrhage can occur even without respiratory symptoms.²⁴ In the present study, the frequency of pulmonary rales in the entire sample was 17%, but in 1994 during an outbreak it reached 40%, which contrasts with the 24% recorded in the 1995–1996 period and 6% in the reference period (1985–1993). Also, the frequency of dyspnea was higher in the 1995–1996 period compared with the reference period (1985–1993) (Table 3). Moreover, the present data showed that clinical characteristics of Weil's disease may be changing, since the presence of arthralgia, dehydration, dyspnea, and pulmonary rales were more frequent in the 1995–1996 period when compared with the 1985–1993 period.

These data suggest that pulmonary involvement in leptospirosis acute renal failure might be becoming more frequent or that the disease, as a whole, is changing. The high frequency of hemoptysis reported during outbreaks or the high prevalence of pulmonary rales in the present study in 1994 could have another explanation, since during outbreaks the number of cases is much higher and hospital facilities do

not increase in the same proportion; thus, only the most severe cases can be hospitalized, giving the impression of a change in the severity of the disease. Contrary to this hypothesis is the fact that renal failure was less severe in 1994 and peak plasma creatinine levels greater than 530 $\mu\text{mol/L}$ were less frequent. However, these hypotheses should be tested by a prospective multicenter study involving various places where leptospirosis is endemic and where outbreaks with pulmonary involvement have been described, as in Korea, India, and Nicaragua.^{8,15,16}

Pulmonary involvement is probably not due to cardiac failure since even when the presence of ECG abnormalities were very common ventricular dysfunction evaluated by 2-dimensional echocardiography was not found.²³ Also, no relationship between interstitial myocarditis and severity of pulmonary lesions was found by Ramachandran and Perera in post-mortem examinations.²⁵ Furthermore, pulmonary involvement may not be due to hypervolemia consequent to oliguric acute renal failure, since no association was found between pulmonary rales and oliguria in the present study. Moreover, in a study in Nicaragua pulmonary hemorrhage was described with no renal involvement or jaundice.¹⁶

In general, reported leptospirosis mortality rate range between 5% and 10%.^{6,8} For hospitalized patients, the reported rates were 18% in French West Indies and 19% in Barbados.^{5,12} Mortality rates for cases in which acute renal failure is present were 26% in Sri Lanka and 18% in São Paulo, Brazil.^{3,10} The mortality rate found in the present study, 22%, is similar to the above-mentioned patients with leptospirosis with acute renal failure.

Recently, Dupont and others studied hospitalized patients with leptospirosis and looked for risk factors for death; they found dyspnea, oliguria, alveolar infiltrates, repolarization abnormalities, and leukocyte counts $> 12,900/\text{mm}^3$ as independent factors associated with death.¹²

In the present study in which only hospitalized patients with leptospirosis with acute renal failure were analyzed, only oliguria was an independent risk factor for death. No conclusions could be made about the effect of treatment with penicillin on the mortality rate because the overall mortality rate was small and only 36% of the patients were treated. No good explanation could be found for the different frequencies of treatment with penicillin over time.

The presence of oliguria as a predictive variable for death caused by acute renal failure due to acute tubular necrosis without leptospirosis has been described in many prospective studies, as in those reported by Liaño and others¹ and Brivet and others.² A previous study carried out by our group (Ávila MO and others, unpublished data) of 879 patients with acute renal failure, only 19 with leptospirosis, showed oliguria as a risk factor for death, and more importantly that a urinary volume $> 1,000 \text{ ml}/24 \text{ hr}$ was a protective factor for death. It is worth noting that all nonoliguric patients in the present study had urinary volumes greater than 1,500 ml/24 hr, which suggests that this characteristic of leptospirosis with acute renal failure could explain a mortality rate lower than the 50–90% found in acute renal failure due to acute tubular necrosis.

Although Everard and others¹³ had shown higher mortality among females than among males (22% and 12%, respectively) in Barbados, in the present study as in that of Dupont

and others,¹² gender was not an independent risk factor for death.^{12,13} This could have occurred as a result of the small number of women studied. However, in the present study, the presence of oliguria was more frequent among females than among males. The higher mortality rate among females could be related to this. Prospective studies with larger number of cases are needed to define the actual role of gender in leptospirosis mortality. In conclusion, our study has shown that in leptospirosis with acute renal failure, oliguria is a risk factor for death and that clinical patterns seem to be changing.

Authors' addresses: Elizabeth Daher and Marcelo Borges Cavalcante, Departamento de Medicina Clínica, Faculdade de Medicina, Universidade Federal do Ceará, Rua Professor Costa Mendes, s/n, Bairro Porangabussu, Fortaleza, CE, Brazil. Dirce M. Trevisan Zanetta, Departamento de Epidemiologia e Saúde Coletiva, Faculdade de Medicina de São José do Rio Preto. Av. Brigadeiro Faria Lima, 5416, CEP 15090-000 São José do Rio Preto, SP, Brazil. Regina C. R. M. Abdulkader, Laboratório de Fisiopatologia Renal, Faculdade de Medicina, Universidade de São Paulo, Av. Dr. Arnaldo, 455. 3o Andar, Sala 3342. CEP 01246-903 São Paulo, SP, Brazil.

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