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Predictors of Lethality in Severe Leptospirosis in Urban Brazil

Anne S. Spichler, **Pedro J. Vilaça**, **Daniel A. Athanazio**, **Jose O. M. Albuquerque**, **Marcia Buzzar**, **Bronislawa Castro**, **Antonio Seguro**, and **Joseph M. Vinetz***
Health Municipality Secretariat of São Paulo, São Paulo, Brazil; Department of Nephrology–LIM 12, University of São Paulo School of Medicine, Brazil; Federal University of Bahia, Brazil; Division of Infectious Diseases, Department of Medicine, University of California San Diego School of Medicine, La Jolla, California

Abstract

To ascertain prognostic factors associated with fatal outcomes in severe leptospirosis, a retrospective case-control study was done using population-based surveillance data. Centralized death certificate reporting of leptospirosis mortality was combined with details of patients' hospitalizations, which were obtained from hospitals representing all sectors of São Paulo city. Among identified leptospirosis cases, 89 lethal cases and 281 survivor cases were analyzed. Predictors of death included age > 40 years, development of oliguria, platelet count < 70,000/μL, creatinine > 3 mg/dL, and pulmonary involvement. The latter was the strongest risk factor with an estimated odds ratio of 6.0 (95% confidence interval: 3.0–12.0). Serologic findings with highest titer against *Leptospira interrogans* serovar Copenhageni did not show significant differences between survivors and non-survivors. Lung involvement was an important predictor of death in leptospirosis in São Paulo, of relevance in leptospirosis-endemic regions where this complication is common.

INTRODUCTION

Leptospirosis is a widespread zoonosis of global distribution caused by pathogenic spirochetes of the genus *Leptospira*. The infection may be transmitted to humans by exposure to urine of infected mammalian reservoirs, such as peridomiciliary rodents or wild and domestic animals.[1,2] The clinical spectrum of leptospirosis ranges from asymptomatic or undifferentiated febrile episodes to severe forms. Severe disease is estimated to occur in 5–15% of all human infections, typically presenting as Weil's syndrome—a triad of jaundice, renal failure, and hemorrhage. The emergence of severe pulmonary hemorrhage syndrome (SPHS) in leptospirosis has recently become of paramount importance, which may present as acute respiratory distress or massive pulmonary hemorrhage with case fatality higher than 50% in many reports.[2] Pulmonary involvement is often overlooked and could be better estimated by autopsy studies.[3] The presentation of leptospirosis seems to be distinct in different geographic areas worldwide. In rural epidemics in Nicaragua and endemic disease in Peru SPHS is uncommon, and presents without classic accompanying features of jaundice and renal failure.[4,5] In the city of Salvador, Brazil, acute renal failure (ARF) is recognized as the major cause of death with absence of

*Address correspondence to Joseph M. Vinetz, University of California San Diego School of Medicine, 9500 Gilman Drive, 0741 Palade Labs, Rm. 125, La Jolla, CA 92093-0741. E-mail: jvinetz@ucsd.edu.
Authors' addresses: Anne S. Spichler, Pedro J. Vilaça, Jose O. M. Albuquerque, Bronislawa Castro, and Antonio Seguro, Department of Nephrology, Laboratory of Basic Research, LIM-12, Faculty of Medicine, University of São Paulo, Av. Dr. Arnaldo 455, Sala 3310, CEP 01246-903, São Paulo, SP, Brazil. Daniel A. Athanazio, Department of Biointeraction, ICS-UFBA, Av. Reitor Miguel Calmon s/no, Campos de Canela, 40. 110-100 Salvador, Bahia, Brazil, E-mail: daa@ufba.br. Marcia Buzzar, Division of Zoonoses, Center for Epidemiological Surveillance, Av. Dr. Arnaldo, 351, 6° Andar, CEP 01246-000 São Paulo, SP, Brazil. Joseph M. Vinetz, University of California San Diego School of Medicine, 9500 Gilman Drive, 0741 Palade Labs, Rm. 125, La Jolla, CA 92093-0741, Tel: +1-858-822-4469, Fax: +1-858-822-5322, E-mail: jvinetz@ucsd.edu.

SPHS.[6] In the city of São Paulo, Brazil, severe and lethal leptospirosis cases usually (72%) share features of Weil's syndrome and SPHS.[7]

Worldwide, independent prognostic factors for lethal outcome in leptospirosis have been found to include older age, oliguria, hyperkalemia, abnormal serum creatinine, acute respiratory distress syndrome (ARDS), pulmonary hemorrhage, elevated bilirubin, hypotension, arrhythmia, and altered mental status.[8–13] However, such studies have typically been hospital-, not population-based. Intrinsic virulence variations among serovars have been claimed to partially explain disease severity albeit mild and severe forms, including SPHS, may be caused by a broad range of pathogenic serovars.[14] Delay between onset and hospitalization have also been highlighted as determinants of poor outcome calling attention for the concern in tropical settings where a primary diagnosis of dengue may delay prompt appropriate antimicrobial therapy.[15]

Leptospirosis remains a reportable illness in Brazil, and is the sixth cause of death among notified infectious diseases in the city of São Paulo, the most populous metropolis of Brazil, with fatality ranging from 11–18% in the period of 2004 through 2006.[7] Because the clinical presentation of leptospirosis varies in different geographic areas, and the fatality rate seems to be increasing in São Paulo, a better understanding of clinical presentation of leptospirosis is needed to enhance its recognition and appropriate treatment. Predictors of lethal outcome must be evaluated in each clinico-epidemiologic setting to consider regional peculiarities. The aim of this study was to estimate the clinical features associated with fatality in severe leptospirosis (in hospitalized patients) in the city of São Paulo, Brazil, where a centralized leptospirosis-related death certificate reporting system allowed us to more comprehensively identify cases of severe leptospirosis on a city-wide population basis.[3]

METHODS

Data collection

A retrospective, case-control study was performed from January 2004 to December 2006, through the Health Coordination Department of the São Paulo Municipality, which obtains leptospirosis surveillance information through death certificate reporting.[3] The protocol included review of medical records, with description of demographic, epidemiologic, clinical, and laboratory information from lethal cases, and survivors who had been hospitalized. Cases were identified in hospitals representing all sectors of the city of São Paulo as follows: South (28% of total; Hospitals Grajau Campo Limpo, Regional Sul, Pedreira, and others); Southwest (10% of total; Heliopolis, Saboia, Ipiranga, Tatuape); North (12% of total; Hospitals Mandaqui, Vila Nova, Hungria, Sao Luiz Gonzaga); West Central (35% of total; Hospitals Emilio Ribas, das Clínicas, University, Santa Casa); and West (15% of total; Hospitals Santa Itaim Paulista, Santa Itaquera, Ermelindo Matarazo, Guainazes, Sao Matheus).

Definitions

Controls (survivors) were defined as having the following: clinical syndrome compatible with leptospirosis (combination of fever, chills, myalgia, jaundice, conjunctival suffusion, renal failure, hemorrhage, pulmonary failure), source of infection for leptospirosis (potential exposure to urine from infected animals on soil, water, flooding), and a laboratory confirmation by either enzyme-linked immunosorbent assay (ELISA) immunoglobulin M (IgM), microscopic agglutination test (MAT) (1 sample > 1:800; seroconversion or 4-fold increase in two exams) or positive culture. Severe disease was defined by requirement for hospitalization plus jaundice, acute kidney injury, and or pulmonary involvement. Cases (lethal cases or non-survivors) were included if the cause of death during hospitalization was directly attributable to complications of leptospirosis. Case confirmation criteria were the same as for survivors

with additional inclusion of patients matching clinical-epidemiologic criteria with pathologic evidence of leptospirosis at necropsy.[7] The selection criteria enrolled all notified and confirmed cases of leptospirosis in the city of São Paulo from 2004 to 2006, and excluded those cases without laboratory confirmation, or not requiring hospitalization. To be included in this study, we selected patients with at least two completed information forms for laboratory tests performed at admission.

A standardized questionnaire was used to collect the following information: age, gender, clinical symptoms (renal failure, jaundice, and pulmonary), risk of exposure, time between onset of symptoms and hospitalization, laboratory results (total bilirubin, platelet count, serum creatinine), and MAT result. For lethal cases, additional information was collected from necropsies and for the period elapsed between hospital admission and death.

Oliguria was defined as urine output less than 400 mL/day. Pulmonary involvement included dyspnea, hemoptysis, pulmonary rales on physical examination, and intubation. Laboratory values were analyzed from the time of admission. The time between onset of symptoms and hospitalization were analyzed in days in both groups. The major risk source of transmission was identified on the basis of the patients' information and domiciliary visits and included reports of direct or visual contact with rats, flooding, and garbage. Autopsy findings were recorded as follows: jaundice, hemorrhage (lung, other involvement), and acute tubular necrosis.

Statistical analysis

Stata (Stata Corp LP, College Station, TX) software was used for analysis. Comparisons between quantitative variables were performed by paired Student's *t* test, and among qualitative variables using the χ^2 test. The relationship between cases and lethal cases was evaluated using logistic regression, with the dependent variable being death. Variables for multivariate analysis were chosen from significant findings from the univariate analysis.

RESULTS

A total of 840 confirmed cases were reported from all sectors of the city of São Paulo, with 711 (85%) requiring hospitalization. Of these cases, 592 (83%) survived and 119 (17%) died. Because we restricted analysis to patients with at least two completed data points for laboratory tests performed on admission, 370 patients were analyzed.

Relevant clinical and other factors associated with fatality were recorded from 370 patients, who met the inclusion criteria: 289 survivors and 89 non-survivors. The completeness of analysis varied according to the variable being measured. Univariate analysis showed that leptospirosis cases were significantly more frequently seen in males than females without differences between the groups (Table 1). Non-survivors were older than survivors (mean, 43 ± 15 years of age), whereas survivors had a mean age of 35 ± 16 years ($P = 0.0001$). Related to clinical parameters, non-survivors presented more frequently with pulmonary involvement and oliguria ($P = 0.0001$), whereas jaundice was not associated with lethal outcome ($P = 0.1$) (Table 1).

The mean period from the onset of symptoms to hospitalization was shorter in lethal cases (5.0 ± 2.7 days) in non-survivors than in survivors (6.0 ± 4.0 days in survivors, $P = 0.02$) (Table 1). The most common reacting serogroup as determined by MAT was Copenhageni, which was detected in 41/89 (46%) of non-survivors and 114/289 (39%) in survivors, but did not significantly differ between these groups (Table 1). Pulmonary involvement (odds ratio [OR], 9.1) oliguria (OR, 7.1), elevated creatinine (> 3 mg/dL; OR, 4.2), elevated total bilirubin (> 6

mg/dL; OR, 2.2), and thrombocytopenia (< 70,000 platelets/μL, OR, 2.6), were associated with lethal outcome (Table 1).

Multivariate analysis showed that over 40 years of age, thrombocytopenia, oliguria, and pulmonary involvement remained independently associated with death (Table 2). The strongest prognostic factor was pulmonary involvement (OR, 6.0; 95% confidence interval [CI], 3.0–12.0), whereas bilirubin > 6 mg/dL did not remain an independent risk factor for lethal outcome.

From 89 non-survivors, 74% had pulmonary involvement detected clinically prior to death. Autopsy was performed in 43 patients, which demonstrated pulmonary hemorrhage in 72%.

The epidemiologic context, in which patients were presumed to contract leptospirosis, was evaluated among non-survivors (71/89) and survivors (222/289), including contact with rodents, flooding areas, and garbage dumps. Rates of reported direct or indirect contact with rodents and exposure to flooding and garbage was common in both non-survivors and survivors, and did not differ between these groups (rodent contact; $P = 0.8$), exposure to flooding, $P = 0.2$; and contact with garbage ($P = 0.5$).

DISCUSSION

In the past decade, there has been a global increase in recognition of the severe pulmonary form of leptospirosis (SPFL) and Weil's syndrome with pulmonary involvement. Previous studies have documented the importance of this form of leptospirosis, but such studies have been biased primarily in being based at one hospital. In the present study, although the analysis was retrospective and hospital-based, cases were identified comprehensively through centralized death certificate reporting and follow-up at many hospitals in all of the sectors of the city of São Paulo. Even though it is probable that some cases of severe leptospirosis were missed, this study nevertheless is the largest and most comprehensive population-based study hitherto reported. Mild and asymptomatic cases of leptospiral infection generally do not present for medical attention in São Paulo (or most endemic regions), thus biasing the patient population analyzed here toward more severe cases. Nonetheless, the present analysis does present a reliable understanding of features that predict lethal outcome in severe leptospirosis.

In São Paulo, Brazil, efforts have been made at the municipal public health to use a surveillance system to identify leptospirosis patterns, especially because case fatality rates and pulmonary involvement seems to be increasing in this region.[6] A death certificate reporting program verifies all suspected lethal cases from São Paulo that include SPFL or in Weil's syndrome. This city-wide, hospital-based, case control study quantified clinically relevant and strong clinical and simple laboratory findings to determine prognostic factors for death in severe leptospirosis.

The frequency of pulmonary involvement in our study was higher than in other reports, which identified dyspnea or pulmonary rales as predictors of death.[8,11] This study population was much larger than a recent study from Reunion Island that reported the highest rate of pulmonary involvement in leptospirosis to date (85%).[13]

The clinical patterns of leptospirosis vary widely among regions in Brazil, where jaundice and renal have predominated. For example, in Salvador, where pulmonary involvement is presented, but less prominent than in São Paulo. The estimation of pulmonary hemorrhage is limited by a lack of necropsy studies in Salvador.[8]

Consistent with previous reports,[8–12,16] we found that age greater than 40 years, oliguria, pulmonary involvement, and thrombocytopenia independently predicted fatality in leptospirosis, with the strongest predictor of death being pulmonary involvement. Similarly,

in Reunion Island, in which respiratory symptoms are detected in 85% of all patients with leptospirosis, acute respiratory failure was the strongest predictor of death.[13] In contrast with reports of epidemic leptospirosis in Nicaragua, where pulmonary hemorrhage in the absence of jaundice occurred, pure respiratory forms of leptospirosis were uncommon in this study (6.5% of all cases). In Iquitos, Peru, seven patients were detected with pulmonary hemorrhage, probably the main cause of death. This under-recognition by physicians has been highlighted and attributable to the lack of typical symptoms, such as jaundice.[5] In the present study, the combined presentation of renal failure and pulmonary involvement occurred in 28% (102/370) of all cases with 55% case fatality. Case fatality for isolated renal and respiratory forms was 18% and 24%, respectively.

Our study has several limitations. Because data were obtained from a population-based surveillance system and death certificate system, some clinical information, such as chest radiographs and blood gases, were not available. On the basis of the high rate of pulmonary hemorrhage at necropsies, it is also possible that milder forms of SPHS may occur in non-survivors that might not be clinically apparent pre-mortem. The SPHS may also present predominantly as acute respiratory distress syndrome and detection of pulmonary hemorrhage may be difficult to detect at the bedside.[2] The discrepancy between jaundice not being a statistically significant predictor of death, whereas measured bilirubin was associated with a severe outcome of leptospirosis, is likely because of the retrospective nature of reporting and recording the clinical signs of illness. Although an active system of surveillance for case confirmation allowed for a large population of patients with confirmed leptospirosis, among 592 confirmed cases in São Paulo from the study period, only 289 had the minimum of two laboratory tests at admission that were consistent with a diagnosis of leptospirosis. Improved medical documentation and ready access to relevant clinical and laboratory information and analysis will be critical for analysis of similar patterns of severe leptospirosis and SPFL in different leptospirosis-endemic and epidemic regions.

Renal failure is a well-established predictor of death in leptospirosis, especially in its oliguric forms.[1] In this study, both oliguria and serum creatinine > 3 mg/dL were found to be independent risk factors for lethal outcome. This is important because it demonstrates that, even in places with a high rate of pulmonary involvement and a high rate of pulmonary hemorrhage as the major cause, renal failure remains an important determinant of outcome.

Conversely, thrombocytopenia as an independent predictor of death has not commonly been observed.[17] Low platelet counts are common in leptospirosis, and human and experimental data have been inconsistent in supporting a role for an underlying disseminated intravascular coagulation process in predisposing to hemorrhagic manifestations in leptospirosis. One potential explanation of thrombocytopenia in leptospirosis is that certain strains of *Leptospira* directly activate platelets; for example, leptospiral proteins that share similarities with human hemostatic factors.[18]

In the present study, a shorter interval between symptoms and hospitalization was associated with lethal outcome. This finding likely reflects more severe presentations; this notion is supported by the frequent finding of SPHS found at autopsy. We did not observe, however, any difference between the periods of symptoms between patients with renal or lung involvement or both syndromes combined. Delay in referral to a specialized infectious disease hospital has been implicated in a higher probability of lethal outcome in Salvador,[15] a place where the major cause of death is ARF.[9] This association between longer periods between onset of symptoms and inpatients and deaths were not observed in some clinical studies where, similar to the conditions of the present study, pulmonary involvement predominates as a major cause of death.[8]

In urban São Paulo, Brazil, renal and pulmonary involvement commonly present together in acute leptospirosis and are important predictors of death. Respiratory involvement was the strongest predictor of death, and the rapid progression of disease and high case fatality rate highlight the urgent need for new therapeutic approaches in severe leptospirosis. The evaluation of predictors of death must be evaluated in different geographic areas taking into account peculiarities of each region.

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TABLE 1

Univariate analysis of demographic, clinical, and laboratory variables

Variables	Non-survivors (n) Mean ± SD or (%)	Survivors (n) Mean ± SD or (%)	Odds ratio	95% confidence interval	*P* value
Sex ratio M:F	5:1 (82% M)	5:1 (84% M)	0.8	0.41–1.59	0.5
Mean age in years	43 ± 15 (89)	35 ± 16 (281)			0.000
Age over 40 years	56%	35%	2.36	1.4–4.0	0.0002
Days of symptoms to admission	5.0 ± 2.7 (89)	6.0 ± 4.0 (281)			0.02
Jaundice	85% (89)	78% (281)	1.6	0.8–3.4	0.1
Mean bilirubin mg/dL	15 ± 13 (89)	10 ± 9 (281)			0.0007
Bilirubin > 6 mg/dL	69%(79)	51% (281)	2.18	1.24–3.8	0.003
Creatinine > 3.0 mg/dL	65% (85)	31% (281)	4.16	2.41–7.20	0.0000
Mean serum ceatinine	4.6 ± 2.4 (89)	2.9 ± 2.2 (281)			0.0000
Platelet < 70,000	61% (65)	36% (258)	2.6	1.5–5.0	0.0000
Mean platelet count	68027 ± 37000 (65)	121000 ± 110000 (265)			0.0005
Pulmonary involvement	74% (89)	26% (281)	9.1	5–17	0.0000
Oliguria	87% (89)	48% (281)	7.1	3.6–15	0.0000
Serogroup icterohaemorrhagiae	92% (41)	80% (114)			0.5

TABLE 2

Multivariate analysis of demographic, clinical, and laboratory variables

Variables	Odds ratio	95% confidence interval	*P* value
Age > 40 years	2.2	1.1–4.3	0.03
Pulmonary involvement	6.0	3.0–12.0	< 0.00001
Oliguria	3.0	1.2–9.0	0.01
Platelets < 70,000	2.2	1.2–4.7	0.01
Creatinine > 3.0 mg/dL	2.3	1.1–5.3	0.03