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Different Patterns in a Cohort of Patients with Severe Leptospirosis (Weil Syndrome): Effects of an Educational Program in an Endemic Area

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Abstract. The aim of this study is to investigate the changes in clinical pattern and therapeutic measures in leptospirosis-associated acute kidney injury; a retrospective study with 318 patients in Brazil. Patients were divided according to the time of admission: 1985–1996 (group I) and 1997–2010 (group II). Patients were younger in group I (36 ± 13 versus 41 ± 16 years, $P = 0.005$) and the numbers of oliguria increased (21% versus 41% in group II, $P = 0.014$). Higher frequency of lung manifestations was observed in group II ($P < 0.0001$). Although increased severity, there was a significant reduction in mortality (20% in group I versus 12% in group II, $P = 0.03$). Mortality was associated with advanced age, low diastolic blood pressure, oliguria, arrhythmia, and peritoneal dialysis, besides a trend to better mortality with penicillin administration. Leptospirosis is occurring in an older population, with a higher number of oliguria and lung manifestations. However, mortality is decreasing and can be the result of changes in treatment.

INTRODUCTION

Leptospirosis is the most important zoonose in the world and its frequency is higher in tropical countries.[1–3] The disease is caused by spirochaete bacteria of *Leptospira* genus, which results from the exposure to urine of infected animals.[4,5] Higher rates of incidence occur during the rainy season.[2,5,6]

The disease begins suddenly with headache, high-degree fever, malaise, myalgia, conjunctival suffusion, and a transient rash. The severe form is characterized by jaundice, acute kidney injury (AKI), and hemorrhage, known as Weil's disease, and it is mainly caused by serovars *Icterohaemorrhagiae*, *Copenhageni*, *Lai*, and others.[7] Renal involvement is characterized by AKI, associated with oliguria and dialysis requirement in severe cases.[8,9] Pulmonary involvement can predominate, and it is the main cause of death.[10]

In Brazil, leptospirosis is endemic, and outbreaks occur during the rainy season, coinciding with localized flooding.[11] The real impact of the disease might be underestimated because many patients with leptospirosis are misdiagnosed as suffering from other infectious diseases, such as dengue or influenza.

Early diagnosis is necessary to institute adequate therapy. Therapy is mainly supportive and many doubts persist in some aspects of treatment, such as antibiotic administration, whereas other uncertain topics have been clarified: early dialysis initiation was associated with a better outcome in leptospirosis-associated AKI.[12]

Associated with treatment evolution, a clinical pattern of leptospirosis seems also to change over time and there are few data on this subject.[13] The aim of this study is to investigate the changes in the clinical pattern of leptospirosis-associated AKI and the effects of general guidelines in management of severe leptospirosis.

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METHODS

Study population. This is a retrospective study with patients admitted to the São José Infectious Diseases Hospital and Walter Cantídio University Hospital in Fortaleza city, Northeast of Brazil, between May 1985 and December 2010, with confirmed diagnosis of leptospirosis (Weil Syndrome) and presence of renal injury by RIFLE criteria.[14] All patients had clinical and epidemiological data suggestive of leptospirosis, and a positive laboratory test for leptospirosis (microscopic agglutination test, higher than 1:800). Patients with diagnosis performed only in the convalescence phase were not included because it was unlikely the result had influenced physician practice.

Definitions. Acute kidney injury was defined according to the RIFLE classification—risk, injury, failure, loss, and end-stage kidney disease.[14] Systolic blood pressure and diastolic blood pressure (DBP) at admission were analyzed. Oliguria was considered to be present when the urinary volume was < 400 mL/day. Dialysis was indicated for those patients who remained oliguric after effective hydration, in those cases where uremia was associated with hemorrhagic or severe respiratory failure, in severe cases or refractory metabolic acidosis and severe or refractory hyperkalemia. Lung manifestation was considered if patients present with dyspnea, pulmonary crackle, hemoptysis, or $pO_2 < 60$ mmHg in arterial blood gas. Hemorrhagic manifestation was considered if patient presented with any petechiae, hematemesis, or hemoptysis.

Patients groups. The patients were divided into two groups according to the years: group I (1985–1996) and group II (1997–2010), and according to the year of admission. These two periods were chosen because there were significant changes in physicians' orientation about patients' treatment after 1996. The main changes were as follows:

1. Early diagnosis: all physicians were oriented to consider leptospirosis diagnosis in patients with fever, jaundice associated with respiratory failure, and/or AKI.
2. Supportive therapy: patients receive crystalloid solutions to restore volume with caution, especially if there were signs of respiratory failure, lung crackles, or hemoptysis.

3. Antibiotic therapy: physicians were oriented to administer penicillin to patients even in later disease presentation.
4. Dialysis therapy: hemodialysis therapy was the preferred method instead of peritoneal dialysis and it was intended to be initiated early after intensive care unit admission and performed daily.

All clinical manifestations and laboratory tests were evaluated. A comparison of clinical and laboratory data was performed between the two groups to investigate if there was any difference in the pattern of leptospirosis presentation in the two periods analyzed. A comparison between survivors and non-survivors in the two periods was also done.

Ethics. The protocol of this study was approved by the Ethical Committee of the Walter Cantídio University Hospital and São José Infectious Diseases Hospital.

Statistical analysis. The results were expressed through tables and summary measures (mean ± standard deviation) in the cases of quantitative variables. All data were analyzed with the programs SPSS version 10.0 (SPSS Inc., Chicago, IL) and Epi Info version 6.04b (Centers for Disease Control and Prevention, Atlanta, GA). Comparison of parameters was done with Student's *t* test, Mann-Whitney, and Fisher's exact test when appropriated. Mann-Whitney test was used for the parameters with a non-normal distribution. Stepwise backward elimination multivariate analysis was performed for the investigation of factors associated with death. All variables presented were considered and it included the factors that presented a significance level < 10% in the univariate analysis. Allocation into the two defined groups was considered an independent variable. P value < 0.05 was considered as statistically significant in all other cases.

RESULTS

A total of 374 patients were evaluated initially. Three hundred eighteen patients were included because they presented with AKI. There were 94 patients in group I and 224 in group II, with an increasing number of cases in the last years (Figure 1). There was a male predominance in both groups (77% and 84.8%, respectively). Patients in group I were younger (36 ± 13 years versus 41 ± 16 years, $P = 0.001$). Diabetes mellitus and hypertension was present in 13 (4.1%) and 27 (8.5%) of all patients with no difference between groups (3.1 versus 4.5%, $P = 0.600$ and 7.4 versus 8.0%, $P = 0.860$, respectively).

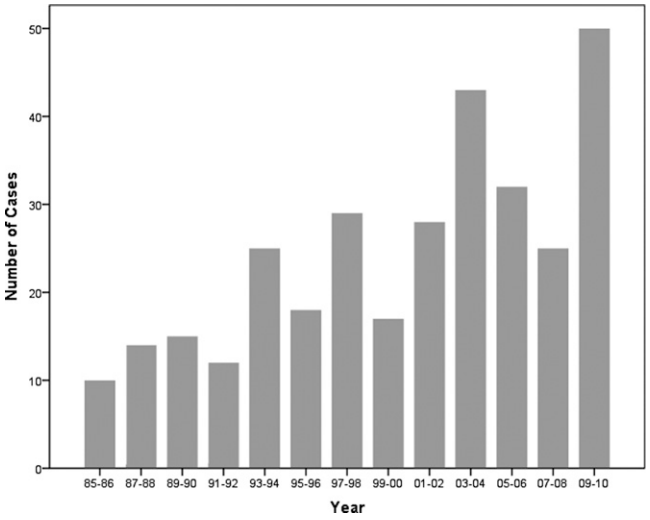

FIGURE 1. Number of patients with leptospirosis-associated acute kidney injury.

TABLE 1
Clinical characteristics of patients with leptospirosis-associated acute kidney injury*

	Group I ($N = 94$)		Group II ($N = 224$)		
	Mean ± SD		Mean ± SD		P
Age	36 ± 13		41 ± 16		0.001
SBP (mm of Hg)	109 ± 19		111 ± 20		0.378
DBP (mm of Hg)	66 ± 15		70 ± 14		0.020
	n	%	n	%	
Gender					
Female	22	23	34	15.2	0.06
Male	72	77	190	84.8	
Symptoms and signs					
Headache	61	64.8	173	77.2	0.002
Fever	92	97.6	213	95.1	0.207
Myalgia	86	91.8	194	86.6	0.179
Vomiting	65	69.4	149	66.5	0.600
Dehydration	57	60.7	139	62.0	0.768
Jaundice	93	98.8	211	94.2	0.569
Hepatomegaly	37	40.0	85	37.9	0.874
Hemorrhagic manifestations	22	23.4	105	46.9	0.001
Respiratory infection	8	9.5	18	8.0	0.896
Calf pain	70	82.4	94	41.8	0.001
Arrhythmias	19	20.2	26	11.6	0.04
Pancreatitis	0	0.0	1	0.4	1.0
Meningitis	2	2.4	1	0.4	0.162
Secondary infections	11	11.8	15	6.7	0.177
Lung manifestation	25	26.6	132	59	< 0.0001
Convulsion	0	0.0	3	1.3	1.0
Splenomegaly	0	0.0	6	2.6	1.0
Obtundation	18	22.0	8	3.6	< 0.0001
Contact with rats	37	39.8	58	25.8	0.06
Oliguria	25	26.5	92	41.1	0.014
Need of dialysis	70	75.0	54	24.1	< 0.0001
Death	19	20.2	27	12.1	0.039

*SBP = systolic blood pressure; DBP = dyastolic blood pressure. Student *t* test and Fisher's exact test. Significant $P < 0.05$.

Serogroup was *Icterohaemorrhagiae* (100%) with serovar *Icterohaemorrhagiae* I 100% of cases and *Copenhageniin* in 59%. No significant difference was observed between the groups. The cases were predominant during the months from March to July. During this period there occurred 76 (81%) cases in group I and 176 (78.5%) in group II. The analysis of the clinical manifestations showed a higher frequency of headache in group II (77% versus 65%, $P < 0.02$), as well as lung (59% versus 26.6%, $P < 0.0001$) and hemorrhagic (46.9% versus 23.4%, $P < 0.0001$) manifestations. Patients in group I had a higher frequency of arrhythmias (20% versus 11.6%, $P = 0.04$) and need of renal replacement therapy (75% versus 24%, $P < 0.0001$), as can be seen in Table 1. The comparison between survivors and non-survivors according to groups can be seen in Tables 2 and 3.

According to the RIFLE classification there was 75 (23.6%) patients in each "Risk" and "Injury" categories, whereas 168 (52.8%) of the patients were classified as "Failure". Mortality was higher in group I in all the classes, but not statistically significant (Table 4). The number of patients in "Failure" was higher in group I (77% versus 42.4%, $P < 0.0001$). The number of patients with oliguria was higher in group II. In group

TABLE 2
Clinical characteristics of patients with leptospirosis-associated acute kidney injury*

	Group I (*N* = 94)					Group II (*N* = 107)				
	Survivors (n-75)		Non-survivors (*N* = 19)			Survivors (n-197)		Non-survivors (*N* = 27)		
	Median [25th–75th]		Median [25th–75th]		*P*	Mean ± SD		Mean ± SD		*P*
Age	32 [24–45]		44 [32–53.5]		0.003	40 ± 15		48 ± 17		0.001
SBP (mm of Hg)	110 [100–120]		100 [90–112.5]		0.038	111 ± 25		111 ± 19		0.896
DBP (mm of Hg)	70 [60–80]		60 [50–65]		0.006	71 ± 13		66 ± 13		0.144
	n	%	n	%		n	%	n	%	
Gender										
Female	11	16.7	8	42.1	0.029	26	13.2	8	29.6	0.041
Male	55	83.3	11	57.9		171	86.8	19	70.4	
Symptoms and signs										
Headache	48	72.7	8	42.1	0.026	146	74.1	21	77.7	0.791
Fever	64	97.0	19	100.0	1.000	190	96.4	23	85.2	0.031
Myalgia	63	95.5	15	78.9	0.041	172	87.3	22	81.5	0.376
Vomiting	43	65.2	16	84.2	0.159	131	66.5	18	66.7	1.0
Dehydration	42	63.6	9	50.0	0.415	78	39.6	12	44.4	0.678
Jaundice	65	98.5	19	100.0	1.000	144	73.1	21	77.8	0.816
Hepatomegaly	25	37.9	9	47.4	0.596	48	24.4	10	37.0	1.0.166
Hemorrhagic manifestations	20	26.7	2	10.5	0.138	89	45.2	16	59.2	0.330
Respiratory infection	5	7.6	3	15.7	0.360	14	7.1	4	14.8	0.167
Calf pain	57	86.4	13	68.4	0.091	86	43.5	8	29.6	0.143
Arrhythmias	9	13.8	8	42.1	0.019	16	8.1	10	37.0	0.001
Pancreatitis	0	0.0	0	0.0	–	1	0.50	0	0.0	1.000
Meningitis	2	3.0	0	0.0	1.000	1	0.50	0	0.0	–
Secondary infections	10	15.2	0	0.0	0.108	13	6.6	2	7.4	0.699
Lung manifestations	18	24.0	7	36.8	0.258	118	59.9	14	51.8	0.496
Convulsion	0	0.0	0	0.0	–	2	1.0	1	3.7	0.254
Splenomegaly	0	0.0	0	0.0	–	6	3.0	0	0.0	1.000
Obtundation	14	21.5	4	23.5	1.000	5	2.5	3	11.1	0.02
Contact with rats	27	65.9	3	25.0	0.019	54	27.4	4	14.8	0.161
Oliguria	12	18.2	13	68.4	< 0.0001	80	40.6	12	44.4	0.704
Need of dialysis	55	74.3	15	75	1.00	39	19.8	15	55.6	< 0.001

* SBP = systolic blood pressure; DBP = dyastolic blood pressure. Student *t* test and Fisher's exact test. Significant $P < 0.05$.

I there were 25 cases of oliguria (26%) and in group II there were 92 patients with oliguria (41.1%), $P = 0.01$.

Antibiotic therapy with Penicillin G was administered in 230 (65%) of the patients, 38 (44%) of them in group I and 192 (86%) in group II ($P < 0.0001$). Jarisch-Herxheimer's reaction was not seen in these patients.

Dialysis was required for 124 cases (39%). The mean number of dialysis sessions was 3.8 ± 2.1 sessions. Among the patients submitted to dialysis, intermittent peritoneal dialysis (IPD) was performed in 63 (50.8%) and daily hemodialysis (DHD) in 61 (49.2%). Mortality was high in patients under IPD versus hemodialysis (22.2% versus 8.2%, $P = 0.03$). The IPD was the predominant method in group I and DHD in group II. Hemodialysis was instituted early (in the first 48 h after admission), whereas peritoneal dialysis was started later (48 h after admission).

TABLE 3
Laboratory characteristics of patients with leptospirosis-associated acute kidney injury, according survivors and non-survivors in both groups*

	Group I (*N* = 94)			Group II (*N* = 107)		
	Survivors (*N* = 75)	Non-survivors (*N* = 19)	*P*	Survivors (*N* = 197)	Non-survivors (*N* = 27)	*P*
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Na_{max} (mEq/L)	132 ± 0.8	131 ± 1.6	0.807	138 ± 0.42	135 ± 1.4	0.007
Na_{min} (mEq/L)	132 ± 0.8	131 ± 1.6	0.875	130 ± 0.43	131 ± 0.9	0.320
$K_{admission}$ (mEq/L)	3.9 ± 0.1	4.1 ± 0.2	0.489	3.9 ± 0.07	3.7 ± 0.14	0.484
K_{min} (mEq/L)	3.1 ± 0.07	3.6 ± 0.192	0.023	3.3 ± 0.04	3.4 ± 0.14	0.421
Ur_{max} (mg/dL)	216 ± 11	207 ± 19	0.541	133 ± 6.5	158 ± 20	0.215
Cr_{max} (mg/dL)	6.4 ± 0.3	6.7 ± 0.6	0.620	4.1 ± 0.2	4.4 ± 0.4	0.534
Arterial pH	7.39 ± 0.01	7.32 ± 0.04	0.123	7.37 ± 0.01	7.36 ± 0.07	0.708
Arterial pO_2	84 ± 22	79 ± 20	0.784	85 ± 16	86 ± 24	0.937
Arterial HCO_3 (mEq/L)	20 ± 1.2	16 ± 1.7	0.126	19 ± 0.5	17 ± 0.91	0.268
Hb (g/dL)	10.3 ± 0.25	10.4 ± 0.36	0.758	11.1 ± 0.1	9.97 ± 0.48	0.010
White blood count ($\times 10^3/mm^3$)	16 ± 14	15 ± 17	0.752	11 ± 0.3	12 ± 1.3	0.347
LDH_{max} (UI/L)	568 ± 53	747 ± 103	0.118	760 ± 68	767 ± 151	0.972
CK_{max} (UI/L)	136 ± 36	400 ± 205	0.283	268 ± 54	356 ± 50	0.412
AST (UI/L)	69 ± 6.8	94 ± 18	0.097	89 ± 9	88 ± 12	0.978
Direct bilirubin (mg/dL)	14 ± 1.4	16 ± 2.3	0.620	9.5 ± 0.7	11.8 ± 2.7	0.364
Indirect bilirubin (mg/dL)	5.5 ± 0.6	6.2 ± 1.0	0.359	4.9 ± 0.4	4.1 ± 1.0	0.878
PT (%)	68 ± 4.0	75 ± 9.1	0.468	68 ± 7.7	70 ± 15	0.789

* Max = maximum values during hospital stay; min = minimum values during hospital stay; Na = sodium; K = potassium; Ur = urea; Cr = creatinine; HCO_3 = bicarbonate; Hb = hemoglobin; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; CK = creatine kinase; PT = prothrombin time.

Table 4
RIFLE classification in patients with leptospirosis-associated acute kidney injury, according groups*

	Group I ($N = 94$)		Group II ($N = 224$)		
	Total	Non-survivors	Total	Non-survivors	P
Risk ($N = 75$)	4	1 (25%)	71	4 (5.6%)	0.24
Injury ($N = 75$)	17	2 (11.7%)	56	6 (10.7%)	0.98
Failure ($N = 168$)	73	16 (21.9%)	95	17 (17.9%)	0.51

*Fisher's exact test. Significant $P < 0.05$.

Overall mortality was 13%. Mortality was significantly higher in group I, and there was a clear reduction in years since 1996 as illustrated in Figure 2. In group I there were 19 deaths (20%) and in group II there were 27 deaths (12%), $P = 0.039$. Factors associated with death were age > 60 years old, DBP below 60 mm of Hg, arrhythmia, and oliguria; whereas hemodialysis was associated with better mortality in relation to peritoneal dialysis. Furthermore, there was a tendency for penicillin to be a protective factor (Table 5).

DISCUSSION

This study is one of the few to investigate the changes in the presentation and evolution of leptospirosis during a large period of time. Patients are getting older and presenting with more lung involvement. Although this greater severity, after implementation of a program mainly based in vigilant hydratation, penicillin administration, early renal substitutive therapy, and preferable hemodialysis instead of peritoneal dialysis, there was an improvement in mortality rates. In multivariate analysis, hemodialysis instead of peritoneal dialysis was associated with decreased mortality, whereas penicillin administration presented a statistical trend to it.

The epidemiology of leptospirosis is changing, reemerging in the large cities in developing countries, where there are proliferations of slums and lack of sanitation.[15] The disease is more frequent among young males, as demonstrated previously in other studies.[16] In our study, we observed an increased number of cases in older individuals that can be a reflection of the aging population, which is a worldwide trend.[17,18] Predominance of male is a known characteristic of leptospirosis and data of the Brazilian Ministry of Health, a total of 4,539 cases were registered in 2006, and 73.7% were male.[19]

There was an increase in the severe forms of the disease, evidenced by the higher frequency of oliguria and symptoms related to lung involvement, such as dyspnea and pulmonary crackles, which can reflect lung involvement and a complication of AKI. There was also a higher frequency of hemorrhagic phenomena, including the appearance of petechiae, hemoptysis, and hematemesis. The higher frequency of manifestations such as oliguria, lung involvement, and hemorrhagic manifestations in the last decade characterizes the more frequent incidence of severe forms of leptospirosis. This severity can be associated with the intensity of immune response on a possible reinfection[20] or inoculum size.[3]

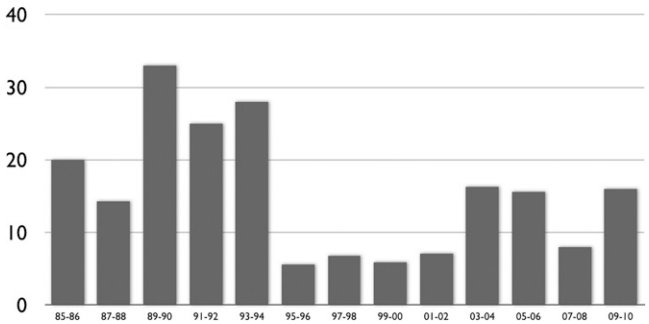

Figure 2. Mortality of patients with leptospirosis-associated acute kidney injury throughout years.

Table 5
Risk factors for death in patients with leptospirosis-associated acute kidney injury*

	OR	Adjusted OR	95% CI	P
Advanced age (> 60 years)	1.697	5.456	1.115–26.706	0.036
Diastolic blood pressure (< 60 mmHg)	2.257	9.555	1.523–59.941	0.016
Oliguria	2.325	10.231	1.930–54.223	0.006
Arrhythmia	1.683	5.383	1.026–28.243	0.047
Hemodialysis (vs. peritoneal dialysis)	–2.630	0.072	0.006–0.811	0.033
Penicillin use	–2.194	0.112	0.018–1.332	0.092

*Out of the model: sex, RIFLE classification, inclusion according group, headache, lung, and hemorrhagic manifestations.
OR = odds ratio; CI = confidence interval.

The use of RIFLE classification showed a higher incidence of severe forms of AKI (patients classified in "Failure") in the first decade, which can be responsible for the higher mortality observed in the first group of patients. In a recent study including critically ill patients with infections, disease-associated AKI (of which 11.6% had leptospirosis), the RIFLE classification was significantly associated with mortality.[21] The mortality was higher in the "Failure" group in the two studied groups in comparison to the "Injury" group. Patients in "Risk" had an even higher mortality in the first group (25%) but because of a small number of patients it is not possible to draw any conclusion.

There was a significant decrease in mortality in the last group (from 20% to 12%), and this can be attributed to a more adequate treatment. Several studies have described a mortality rate near 20%,[22,23] which was similar to what we observed in the first group in our cohort. The risk factors for death in these studies were age > 40 years, dyspnea, oliguria, elevated white blood cell count, repolarization abnormalities on electrocardiograms, and alveolar infiltrates on chest radiographs.[23,24] In this study, we found oliguria, arrhythmias, lower DBP, and age as independent risk factors for death. We believe that those factors associated with mortality reflect severity of the disease evolution. Arrhythmias, for instance, was more frequent in group I and it was associated with mortality, suggesting it is a marker of severity as demonstrated by others.[24] The higher mortality observed in the first group can be caused by differences in treatment protocols as evidenced by the protective effect of hemodialysis in comparison with peritoneal dialysis and the trend in association between survival and penicillin usage. In the second group, these factors were implemented more frequently and the higher survival rate can be attributed to this clinical approach.

An important phase in the treatment of leptospirosis-associated AKI is hydration. Hypotension and hypovolemia are important factors that lead to renal dysfunction in leptospirosis and venous hydration is crucial to patients' improvement. Recent studies show that hydration should be done with caution, because there is a high risk for pulmonary congestion and

deterioration of lungs, which are generally involved in severe leptospirosis with hemorrhagic manifestations.[25] A change in the approach we used for our patients was done at the end of the 1990s decade, with a cautious hydration. Even with a vigilant hydratation approach, fewer patients needed dialysis. This is in accordance with recent observations that overzealous fluid therapy is associated with worse renal function.[26] Unfortunately, it is difficult and imprecise to measure fluid balance in a retrospective study.

Early dialysis is of huge importance in leptospirosis and is associated with a significant decrease in mortality.[12] Recent studies show that the early institution of dialysis and daily dialysis is beneficial and decreases mortality.[12] Dialysis was required for a lower number of patients in the second group, which contradicts the severity of disease, but this can be caused by an adequate and efficacious institution of conservative treatment of leptospirosis associated-AKI and correct indication of dialysis. We observed a change from peritoneal dialysis to hemodialysis in the second period. Hemodialysis was done earlier (in the first 48 h after admission), and this could be responsible for the reduction in mortality. Antibiotic use was administered to a higher percentage of cases in the second group (86% versus 44%), which could also have influenced the mortality reduction. Antibiotic use is still controversial in leptospirosis, but some recent studies reported favorable outcomes in leptospirosis patients treated with penicillin.[27,28]

This study has several limitations. First, its retrospective nature does not permit a conclusion on which intervention changes were really associated with a better outcome, although multivariate analysis suggests it. Second, there is a lack of data about diuretic usage in oliguric patients. However, we know the lack of impact in mortality of transforming an oliguric AKI into a non-oliguric one.[29] Third, it is the inability to access fluid balance and its association with renal function, a need of dialysis and mortality.

In summary, leptospirosis is occurring in an older population, with an increase in severity, as evidenced by an increase in oliguric cases, pulmonary, and hemorrhagic manifestations. Risk factors for death were oliguria, lower DBP, arrhythmia, and age. Of importance, we detected that therapeutic measures are associated with better survival.

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