Leptospirosis Guideline
-Renal Part-
The Philippine Society of Nephrology

DISCLAIMER: This document is not the official release of the Leptospirosis Guideline and is provided for information and guide only in managing our leptospirosis cases. The final version of the Leptospirosis Guideline will be released and published as soon as adopted.

LEPTOSPIROSIS- ASSOCIATED ACUTE KIDNEY INJURY
Statement One:

Original:

Acute kidney injury (AKI) is one of the major complications of leptospirosis. The incidence varies from 10 % to 60 %.[1-5] Its presence is a marker of severity and is an indication for hospitalization as it may portend a poorer prognosis.

Revision:
Acute kidney injury (AKI) is one of the major complications of leptospirosis. The incidence varies from 10 % to 70%.[1-7] Its presence is a marker of severity and is an indication for hospitalization as it may portend a poorer prognosis.

Statement Two:
Diagnosis of Leptospirosis-associated Acute Kidney Injury (AKI)

Original:
1. What are the clinical features of AKI due to leptospirosis?
The features may span from mild proteinuria to severe anuric acute renal failure.[6] Commonly it may present as non-oliguric renal failure with mild hypokalemia. [7] Oliguria with hyperkalemia may reflect the severity of AKI and may connote poor prognosis.

The underlying pathology in renal leptospirosis is a combination of acute tubular damage and tubule-interstitial nephritis.[8] The presence of tubular dysfunction usually predisposes the patient to hypokalemia and polyuria.[9] Acute kidney injury that is severe enough to manifest with oliguria and hyperkalemia portends a poorer prognosis.

Revision:
The features may span from sterile pyuria , tea colored urine, mild proteinuria to severe anuric acute renal failure.[8-10] Commonly it may present as non-oliguric renal failure with mild hypokalemia. Oliguria with hyperkalemia may reflect the severity of AKI and may connote poor prognosis.

The underlying pathology in renal leptospirosis is a combination of acute tubular damage and tubule-interstitial nephritis.[11] The presence of tubular dysfunction usually predisposes the patient to hypokalemia and polyuria.[12] Tubular function abnormalities precede a decline in the glomerular filtration rate, which could

explain the high frequency of hypokalemia .[13] Acute kidney injury that is severe enough to manifest with oliguria and hyperkalemia portends a poorer prognosis.

Statement 3:
2. What are the recommended laboratory tests for AKI?

Original:
CBC and plt, Blood Urea Nitrogen, Creatinine, Sodium, Potassium, Urinalysis, SGPT, SGOT, billirubi, ABG and Chest x-ray are recommended.

Creatinine generally indicates the level of kidney function. Creatinine > 3mg / dL together with age > 40 years, oliguria, platelet count < 70,000 u / L and pulmonary involvement are predictors of mortality in severe leptospirosis.[10]

Hyponatremia and hypokalemia are common findings due to tubular dysfunction. Abnormal urine findings include pyuria, hematuria, proteinuria and crystalluria.[11]
Chest x-ray is indicated when ARDS or pulmonary hemorrhage is suspected.
Urine or serum NGAL (if available) will increase in ATN ahead of serum creatinine by at least two days[12] and will help differentiate ATN from pre-renal azotemia.[13] In acute kidney injury, serum creatinine rises rather late in the process, and so there has been an effort to identify biomarkers, such as urine or serum NGAL that indicate acute kidney injury much earlier.
Revision:
CBC, plt, BUN, creatinine, sodium, potassium, urinalysis, ast, alt, bilirubin and chest x-ray are recommended.
Neutrophilia and thrombocytopenia are associated with increase death in leptospirosis.[14]
Creatinine generally indicates the level of kidney function. Creatinine > 3mg / dL together with age > 40 years, oliguria, platelet count < 70,000 u / L and pulmonary involvement are predictors of mortality in severe leptospirosis.[15]

Severe cases of leptospirosis had a BUN/creatinine of < 15 upon initial assessment
Hyponatremia and hypokalemia are common findings due to tubular dysfunction. Abnormal urine findings include pyuria, hematuria, proteinuria and crystalluria.[16]
Elevated bilirubin and liver enzymes are indication of severe acute renal failure in leptospirosis.[14]

Chest x-ray is indicated when ARDS or pulmonary hemorrhage is suspected.

Statement 4:

Original:

3. What is oliguria and what are the predictors of oliguric AKI?

Oliguria is defined as urine output < 0.5 mL/kg/hr or <400mL/day[8] or a self report of decreased or no urine output within the last 12 hours

In a retrospective study of 196 patients in Brazil with leptospirosis-associated AKI, predictors for developing oliguric AKI in leptospirosis on univariate analysis included age > 40 years, crackles, low arterial ph, hyponatremia, increased serum creatinine, elevated direct bilirubin and AST levels.[13] On multivariate analysis, the independent predictors for developing oliguric AKI were presence of crackles (OR 5.3, 95%CI 1.78 to 13.35) and elevated direct bilirubin (OR 1.08, 95% CI 1.005 to 1.087).[13]

In a prospective study of acute renal failure secondary to leptospirosis at the Philippine General Hospital from 1992-95, predictors for oliguria identified on multivariate analysis of 187 patients were: elevated creatinine, low bicarbonate, thrombocytopenia and low alkaline phosphatase.[15] An earlier retrospective study of 191 patients with leptospirosis-induced acute renal failure at the Philippine General Hospital from 1985-91 showed that high levels of SGOT, SGPT, creatinine, low levels of bicarbonate and maximum urine output of <1,996cc/24 hrs were associated with poor prognosis.[16]

Revision:

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associated with poor prognosis.[16]

In a retrospective study of Evaluation of clinical monitoring device for predicting outcomes in leptospirosis at the University of Santo Tomas from 1979-1993, reliable predictors of clinical outcome in leptospirosls in 104 patients were: presence of hemorrhage, jaundice (more importantly the duration) and urine output. [2]

Statement 5:
Original:
4. What are the symptoms and signs of hypovolemia?
a. Thirst
b. Dry mucosal membranes and axillae [SEP]
c. Poor skin turgor especially over the sternum [SEP]

Revision:
4. What are the symptoms and signs of hypovolemia?
a. Thirst
b. Dry mucosal membranes and axillae [SEP]
c. Poor skin turgor especially over the sternum
d. Hypotension (postural), tachycardia
e. Oliguria
f. Reduced jugular venous pressure

Symptoms related to volume depletion induced by hypovolemia are primarily related to decreased tissue perfusion. Earliest complaints include thirst. Patients may report with decreased urine volume or frequency.

Physical examinations that suggest volume depletion due to decrease in the interstitial volume can be detected by the examination of the skin and mucous membranes.
The elastic property, called turgor is partially dependent upon the interstitial volume of the skin and subcutaneous tissue. However, elasticity diminishes with age and so poor skin turgor cannot be used in older patients (more than 55 to 60 years old). In older patients , skin elasticity is best preserved on the inner aspect of the thighs and skin overlying the sternum.
Salivary secretions are diminished in volume depleted patients

A decrease in plasma volume can lead to reductions in systemic blood pressure and venous pressure in jugular veins.

The arterial blood pressure changes from near normal with mild hypovolemia to low in the upright position. Progression of volume depletion will result to persistently low arterial pressure regardless of posture.

Venous pressure can be estimated accurately by physical examination. The height of the jugular venous pulse above the right atrium (5-6 cm above the sternal angle of Louis) approximates the arterial pressure. We interpret the venous pressure as either low (less than or equal to 5 cm H_2O) or high (greater than or equal to 10 cm H_2o)

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Journals:

Supporting Journals: Statement 1 .

A: Of a total of 125,243 admissions, 35 patients were admitted with confirmed leptospirosis. Twenty-three patients (65.7%) developed AKI.

AKI is common in leptospirosis with an incidence of 65.7% but with a favorable outcome where 78.3% have a complete AKI recovery. Male gender appeared to be a risk factor of developing leptospirosis associated AKI.

B: The incidence of acute kidney injury ranges from 10-60%.
Factors associated with the Need for Renal Replacement Therapy in Leptospirosis: A Retrospective Cohort St Hernandez, Aylmer Rex B., et al

C. Although a rare cause of acute renal failure (ARF) in the majority of developed countries, leptospirosis is re- ported as causing 24–32% of ARF cases in tropical countries such as Thailand and Singapore [1]. The frequency of ARF among hospitalized patients with leptospirosis varies from 16 to 79% depending on ARF definition [2–4].

D. Available literature from other Asian countries showed leptospiral renal failure to be as high as 44 - - 67%.' Daysog in an i l-year study of 79 acute renal failure cases reported a frequency of 12.9%.

Evaluation of Clinical Monitoring Device for Predicting Outcomes in Leptospirosis. Melvin R. M**a**rcial, M.D., Emm**a**nu**e**l Edwin R. Dy, M.D. , Angeles-Tn-Alora, Remedios Fabra-Coronel. *Phil*. *J*. *Intern**a**l Medicin*e, *34:227-234*. *N**o**v. Dec*. *1996*

Support Journals: statement 2

A: Fever was absent in only 3 cases while anorexia was present in all. Malaise, abdominal pain, **highly colored urine**, headache and vomiting were also seen indecreasing order of frequency.Twenty patients (19.2%) were anuric on admission.
Daysog in an i l-year study of 79 acute renal failure cases reported a frequency of 12.9%. In this institution, Alora in 1971 and Manaloto in 1978 had] 7.6% and 68.9% incidences of acute renal failure, respectively, In this study, 74% had acute renal failure, 58.4% of whom had the oliguric type. On the other hand, However observed that a **serum creatinine level of 3**

mg/dL or more was associated with mortality of 64% 6 compared to the present yield of 24%. Creatinine itself is nontoxic; how- ever, its conversion to sarcosine and methylguanine may cause toxic effect on uremic patients. The high creatinine level, as well as renal type of BUN/creatinine usually alarms physicians of probable poor outcome and need for dialysis.

Evaluation of Clinical Monitoring Device for Predicting Outcomes in Leptospirosis. Melvin R. M**a**rcial, M.D., Emm**a**nu**e**l Edwin R. Dy, M.D. , Angeles-Tn-Alora, Remedios Fabra-Coronel. *Phil. J. Intern**a**l Medicin*e, *34:227-234*. *N**o**v..Dec*. *1996*

B. The most common clinical features were conjunctival suffusion and myalgia, followed by abdominal pain and **oliguria**.

Outbreak of Leptospirosis after Flood, the Philippines, 2009 Al-shere T. Amilasan et al, Emerging Infectious Diseases · January 2012

C. Microalbuminuria was defined as a urinary albumin-to-creatinine ratio of 30 mg/g or higher using the first-morning urine. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which is more accurate than the Modification of Diet in Renal Disease Study equation

Overlooked Risk for Chronic Kidney Disease after Leptospiral Infection: A Population- Based Survey and Epidemiological Cohort Evidence Huang-Yu Yanf et al. PLoS Negl Trop Dis 9(10): e0004105. doi:10.1371/journal.pntd.0004105

D. Among these patients, 64 (32.6%) were oliguric and 132 (67.4%) non-oliguric.

Predictors of Oliguric Acute Kidney Injury in Leptospirosis A Retrospective Study on 196 Consecutive Patients Elizabeth F. Daher[a, b] Geraldo B. Silva, Jr.[a] Nahme N.N. Karbage[a] Paulo C. Carvalho, Jr.[a] Raquel S. Kataoka[a] Eveline C. Silva[a] Max M. Magalhães[a] Rosa M.S. Mota[c] Sônia M.H.A. Araújo[a] Oswaldo A. Gutiérrez-Adrianzén[a] Alexandre B. Libório[a, b, d]

E. The renal involvement in leptospirosis can vary from a subclinical course, with **mild proteinuria and abnormal urinary sediments** to an **overt AKI.** The AKI usually presents with a rapid elevation in blood urea and creatinine, and can be associated with jaundice. Kidney injury in patients with

hyperbilirubinemia represents a severe form of the disease frequently accompanied by oliguria or anuria

Sitprija V, Losuwanrak K, Kanjanabuch T: Leptospiral nephropathy. Semin Nephrol 2003, 23:42–48.

F. Based on the presence of jaundice and impaired renal function, the disease in these patients was considered severe. Switching off the compensating mechanism by volume expansion alone can be dangerous for fluid overload because of the decreased response to water load.[8,12] There is a high incidence of acute respiratory distress syndrome in the patient with leptospirosis.

CLINICAL STUDY Leptospiral Acute Renal Failure: Effects of Dopamine and Furosemide Kannikar Niwattayakul Department of Medicine, Loei Hospital, Loei, Thailand 2007

G. Signs and symptoms on admission decrease **urine output (p=0.0000) , dysuria (p= 0.155) , tea colored urine (p=0.3196)**

Factors associated with the Need for Renal Replacement Therapy in Leptospirosis:
A Retrospective Cohort St Hernandez, Aylmer Rex B., et al

H. **Anuria** on admission was seen in 20 patients (19.2%). Seventy-nine (74%) had acute **renal failure,** 45 (58.4%) of whom had the **oliguric type. Highly colored urine was seen in 71 (68.3%)** and 13 (12.5%) had **dysuria.** Costovertebral angle tenderness was seen in 12 (11.5%). Seventy-five cases (97%) with acute renal failure were noted to be jaundiced

Leptospirosis Revisited at the Santo Tomas University Hospital .Melvin R. Marcial, M.D.,* Emmanuel Edwin R. Dy, M.D.** and Angeles Tan-Alora, M.D.*** Phil J Microbiol Infect Dis 1994; 24(1):21-33]

I All patients presented with jaundice, fever and myalgia. Bilirubin and creatine kinase were higher in group 1. **Oliguria** was observed in 11% of all patients and 49% required dialysis; all these patients were from group 1. All renal parameters were normal at the 6th month except U/P_{osm} that remained lower than normal. The pattern of renal function recovery was similar in both groups except for urinary volume.

Pattern of Renal Function Recovery after Leptospirosis Acute Renal Failure Elizabeth De Francesco Daher et al. Nephron Clin Pract 2004;98:c8–c14

J. Leptospirosis ARF has peculiar characteristics: usually it is **nonoliguric and**

hypo- or normokalemic. Clinical and experimental studies have shown that these characteristics are due to a preferential proximal tubular lesion and to a medullar collecting duct resistance to vapressin [5]. The vasopressin resistance would be responsible for the non-oliguria. The proximal tubular lesion would induce decrease in sodium reabsorption with con- sequent increase in distal potassium secretion determined by distal increased sodium load, high urinary flow and increased levels of plasma cortisol and aldosterone [4]. Also thick ascending limb dysfunction and distal tubular acidosis have been described.

Pattern of Renal Function Recovery after Leptospirosis Acute Renal Failure
Elizabeth De Francesco Daher et al. Nephron Clin Pract 2004;98:c8–c14

K. As reported by other authors, **oliguria** in leptospirosis is caused mainly by dehydration: 91% of our patients were dehydrated at admission but after appropriate hydration only 11% were oliguric [2, 7, 17].

Pattern of Renal Function Recovery after Leptospirosis Acute Renal Failure
Elizabeth De Francesco Daher et al. Nephron Clin Pract 2004;98:c8–c14

Support Journals: statement 3:

A. **Anemia** was seen in only 24 case**s** (23%) despite presence of overt bleeding in 58 patients (55,8). Majority of the study population had normal white blood cell count. Significant **albuminuria, cylindruria and hematuria** w**e**re the m**o**st c**o**mmon urinalysis findings. Significant pyuria with bacteriuria were seen in 86 cases (82.7%) %) only

A creatinine level > 5 mg% on admission was seen in 54 - 57.9% of the subjects while a normal level w**a**s n**o**ted. Average creatinine level on admission was 5.55 +/k 3.9 mg% while mean discharge level was 2.5 +/- 2.8 rag

Bl**o**od ure**a** nitr**o**gen **l**evel (BUN) on admissi**o**n w**a**s n**o**ted to be more than 5 times the n**o**rm**a**l in 46 cas**e**s (44.2%) and only 30 c**a**ses (28.8%) had norm**a**l v**a**lues. Aver**a**ge BUN **l**ev**e**l on admissi**o**n was 56.5 +/- 36**.**7 mg%

Severe cases had a **B**UN/cre**a**tinine of < 15 up**on** initial **a**ssessment.
Evaluation of Clinical Monitoring Device for Predicting Outcomes in Leptospirosis. Melvin R. M**a**rcial, M.D., Emm**a**nu**e**l Edwin R. Dy, M.D. , Angeles-Tn-Alora, Remedios Fabra-Coronel. *Phil*. *J*. *Intern**a**l Medicin*e, *34:227-234*. *N**o**v*.*.Dec*. *1996*

Creatinine clearance, fractional excretion of sodium and potassium, proteinuria and sodium proximal reabsorption were measured under normal sodium diet. Urinary pH and the ratio urinary to plasma osmolality (U/P_{osm}) were measured 18 h after food and water withdrawal.

Pattern of Renal Function Recovery after Leptospirosis Acute Renal Failure
Elizabeth De Francesco Daher et al. Nephron Clin Pract 2004;98:c8–c14

At admission, hyperkalemia was observed in only 1 patient, while hypo- kalemia was present in 57% of our patients. These data confirm that leptospirosis ARF is usually nonoliguric and hypokalemic [7].

Pattern of Renal Function Recovery after Leptospirosis Acute Renal Failure
Elizabeth De Francesco Daher et al. Nephron Clin Pract 2004;98:c8–c14

Besides dehydration, jaundice and rhabdomyolysis are other factors involved in the pathogenesis and severity of leptospirosis ARF [4, 5]. All our patients had important jaundice with bilirubin levels up to 855 Ìmol/l. These data point to the severity of ARF as part of a more severe clinical condition as a whole, since group 1 presented more severe jaundice, leukocytosis and rhabdomyolysis. Besides the direct action of *Leptospira* in the kidney, jaundice, rhabdomyolysis and dehydration in leptospirosis are factors that can worsen ARF.

Pattern of Renal Function Recovery after Leptospirosis Acute Renal Failure
Elizabeth De Francesco Daher et al. Nephron Clin Pract 2004;98:c8–c14

Experimental studies showed that histological lesions are more intense and more precocious in the proximal tubules [14, 22]. Functional studies in guinea pigs showed indirectly that decreased sodium proximal absorption occurs even in infected animals with normal GFR [22]. However, studies in human leptospirosis to evaluate proximal tubular impairment are few and controversial. Lin et al. [23] studying the tubular function of one patient in the **recovery phase of leptospirosis ARF with normal GFR but with increased kaliuresis, and consequent hypokalemia and metabolic alkalosis,** found normal proximal function (non-bicarbonaturia, glucosuria, phosphaturia or uricosuria) and attributed the inappropriate kaliuresis to a defective thick ascending limb of Henle. However, Liamis et al. [24] and Liberopulos et al. [25], studying one patient each with

leptospirosis and normal P_{creat}, reported proximal tubular dysfunction mimicking Fanconi syn- drome – phosphaturia, uricosuria, and renal glycosuria. Yang et al. [6] studying 4 patients at the recovery phase of leptospirosis ARF reported proximal tubular defects in 1, thick ascending limb of Henle dysfunction in 2, and nor- mal tubular function in 1 patient. Seguro et al. [7] analyz- ing prospectively 11 patients with leptospirosis **ARF on the 1st and 8th day of hospitalization found that sodium and potassium excretion and urinary potassium to sodium ratio that were increased on the 1st day**, concomitantly decreased on the 8th day.

> Pattern of Renal Function Recovery after Leptospirosis Acute Renal Failure
> Elizabeth De Francesco Daher et al. Nephron Clin Pract 2004;98:c8–c14
> 6 Yang CW, Wu MS, Pan MJ: Leptospirosis renal disease. Nephrol Dial Transplant 2001; 16(suppl 5):73–77.

7 Seguro AC, Lomar AV, Rocha AS: Acute renal failure in leptospirosis. Nonoliguric and nonol- iguric and hypokalemic forms. Nephron 1990; 55:146–151.

14 Faine S, Adler B, Bolin C, Perolat P: *Leptospira* and leptospirosis, ed 2. Melbourne, Victoria. Australia, MediSci, 1999.

22 Arriaga AJD, Rocha AS, Yasuda PH, de Brito T: Morpho-functional patterns of kidney injury
in the experimental leptospirosis of the guinea pig *(L. icterohaemorrhagiae)*. J Pathol 1982; 138:145–161.

23 Lin CL, Wu MS, Yang CW, Huang CC: Lepto- spirosis associated with hypokalaemia and thick ascending limb dysfunction. Nephrol Dial Transplant 1999;14:193–195.

25 Liberopoulos E, Bairaktari E, Elisaf M: Revers- ible proximal tubular dysfunction in a patient with acute febrile illness, marked hyperbiliru- binemia and normal renal function: Evidence of leptospirosis. Nephron 2002;91:532–533.

Of the initial laboratory findings, neutrophilia, thrombocytopenia, increased blood urea nitrogen, and increased creatinine levels were associated with death.

Outbreak of Leptospirosis after Flood, the Philippines, 2009
Al-shere T. Amilasan et al, Emerging Infectious Diseases · January 2012

Risk factors for fatal leptospirosis were jaundice, anuria, and hemoptysis at admission. These are typical signs of the severe form of leptospirosis called Weil disease (*11*), confirming earlier work (*12*,*13*). Hemoptysis with high CFR (7 [47%] of 15) may have represented leptospirosis- associated severe pulmonary hemorrhagic syndrome (*14*). Some clinical features, including cough, seemed to be associated with lower risk for death, but minor symptoms in dying patients might have been

overlooked. High leukocyte counts, blood urea nitrogen and creatinine levels, and lower platelet counts were also associated with death.

Outbreak of Leptospirosis after Flood, the Philippines, 2009
Al-shere T. Amilasan et al, Emerging Infectious Diseases · January 2012

elevated urea (63.9%) and creatinine levels (53%). Serum creatinine values of more than 1.4 mg/dl were found in more than half of the patients

Leptospirosis in Coastal South India: A Facility Based Study
Ramesh Holla,[1] Bhagwan Darshan,[1] LatikaPandey,[2] Bhaskaran Unnikrishnan,[1] Nithin Kumar,[1]Rekha Thapar,[1] Prasanna Mithra,[1] and VamanKulkarni[1]

acute kidney injury (AKI) OR = 2.90 (95%CI 1.31–6.15), hypokalemia (<3.5) with hyponatremia (< 135) OR = 3.56 (95%CI 1.17–10.84)
Thai-Lepto-on-admission probability (THAI-LEPTO) score as an early tool for initial diagnosis of leptospirosis: Result from Thai-Lepto AKI study group Theerapon Sukmark,, et al March 19, 2018

with normal or slightly decreased serum potassium.

Predictors of Oliguric Acute Kidney Injury in Leptospirosis: A Retrospective Study on 196 Consecutive Patients Elizabeth F. Daher[a, b] Geraldo B. Silva, Jr.[a] Nahme N.N. Karbage[a] Paulo C. Carvalho, Jr.[a] Raquel S. Kataoka[a] Eveline C. Silva[a] Max M. Magalhães[a] Rosa M.S. Mota[c] Sônia M.H.A. Araújo[a] Oswaldo A. Gutiérrez-Adrianzén[a] Alexandre B. Libório[a, b, d]

Other prognostic factors in leptospirosis include respiratory insufficiency, **metabolic acidosis**, cardiac abnormalities (arrhythmias, repolarization disturbances), hypotension, **hyperkalemia**, thrombocytopenia, hyperbilirubinemia, leukocytosis and anemia

Predictors of Oliguric Acute Kidney Injury in Leptospirosis: A Retrospective Study on 196 Consecutive Patients Elizabeth F. Daher[a, b] Geraldo B. Silva, Jr.[a] Nahme N.N. Karbage[a] Paulo C. Carvalho, Jr.[a] Raquel S. Kataoka[a] Eveline C. Silva[a] Max M. Magalhães[a] Rosa M.S. Mota[c] Sônia M.H.A. Araújo[a] Oswaldo A. Gutiérrez-Adrianzén[a] Alexandre B. Libório[a, b, d]

The serum creatinine ranged from 2.4 to 5.0 mg/dL; blood urea nitrogen from 42 to 103 mg/dL; fractional excretion of sodium (FENa) from 1.21 to 2.08%; and total

serum bilirubin from 3.9 to 9 mg/dL.

CLINICAL STUDY Leptospiral Acute Renal Failure: Effects of Dopamine and Furosemide Kannikar Niwattayakul Department of Medicine, Loei Hospital, Loei, Thailand 2007

Plasma concentrations of urea (180±111 ; 187±95), creatinine (P_{cr} - 4.8±2.5 ; 5.7±2.7), potassium (P_K - 3.3±0.5; 3.2±0.6), sodium (P_{Na})- 130±5 ;130±6) serum albumin (2.7±0.5; 2.9±0.4) , arterial gasometer(20±4), 24 hour proteinuria (U_{prot} 840±610* ; 454±246) were dosed on admission and three times a week during hospitalization.

EVALUATION OF PENICILLIN THERAPY IN PATIENTS WITH LEPTOSPIROSIS AND ACUTE RENAL FAILURE
Elizabeth De Francesco DAHER(1,2) & Charlys Barbosa NOGUEIRA(1) 2000
The laboratory parameters associated with the need for RR are elevated BUN (OR=5.10 [95% CI 2.29-11.34]), elevated creatinine (OR=13.98 [95% CI 5.97-32.70]), elevated potassium (OR=2.44 [95% CI 1.19-5.01]), decreased bicarbonate (OR=2.60 [95%1.17-5.76]) and decreased platelet (OR=2.175 [95% CI 1.34-5.65)}.

Factors associated with the Need for Renal Replacement Therapy in Leptospirosis: A Retrospective Cohort Study Hernandez, Aylmer Rex B., et al
Significant albuminuria, cylindruria and hematuria were the most common urinalysis findings (Figure 17.1). Significant pyuria with bacteriuria were seen in 86 cases (82.7%); however, bacteriologic isolation was seen in only 8 cases, A creatinine level > 5 mg% on admission was seen in 54 (57.9%) of the subjects while a normal level was noted in 28 cases (26.9%) only. Average creatinine on admission was 5.55 + 3.9 mg% while level on discharge was 2.5 + 2.8 mg% (Figure 17.2).

Blood urea nitrogen level (BUN) on admission was noted to be more than 5 times the normal in 46 cases (44.2%) and only 30 cases (28.8%) had normal values. Average BUN level on admission was 56.5 + 36.7 mg% while mean BUN level on discharge was 31.7 ± 23.9 mg%. Seventy cases (67.3%) had a BUN/ creatinine of < 15 upon initial assessment.

Leptospirosis Revisited at the Santo Tomas University Hospital .Melvin R. Marcial, M.D.,* Emmanuel Edwin R. Dy, M.D.** and Angeles Tan-Alora, M.D.*** Phil J Microbiol Infect Dis 1994; 24(1):21-33]

Four different biomarkers were applied in 2011, including serum and urine neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule–1 creatinine ratio (KIM–1/Cr), and monocyte chemoattractant protein–1 (MCP–1).

Overlooked Risk for Chronic Kidney Disease after Leptospiral Infection: A Population- Based Survey and Epidemiological Cohort Evidence Huang-Yu Yanf et al. PLoS Negl Trop Dis 9(10): e0004105. doi:10.1371/journal.pntd.0004105

Support Journals: Statement 4:
Markers for oliguria were age higher than 40 years (OR = 1.02, p = 0.04), hyponatremia (OR = 0.94, p = 0.03), elevated serum creatinine (OR = 1.11, p = 0.04), low arterial pH (OR = 1.0002, p = 0.01), high levels of AST (OR = 1.005, p = 0.01), crackles (OR = 3.83, p ! 0.001) and direct bilirubin (OR = 1.03, p = 0.03). Independent markers for oliguria were crackles (OR = 5.17, p = 0.0016) and direct bilirubin levels (OR = 1.051, p = 0.04).

Predictors of Oliguric Acute Kidney Injury in Leptospirosis A Retrospective Study on 196 Consecutive Patients Elizabeth F. Daher[a, b] Geraldo B. Silva, Jr.[a] Nahme N.N. Karbage[a] Paulo C. Carvalho, Jr.[a] Raquel S. Kataoka[a] Eveline C. Silva[a] Max M. Magalhães[a] Rosa M.S. Mota[c] Sônia M.H.A. Araújo[a] Oswaldo A. Gutiérrez-Adrianzén[a] Alexandre B. Libório[a, b, d]

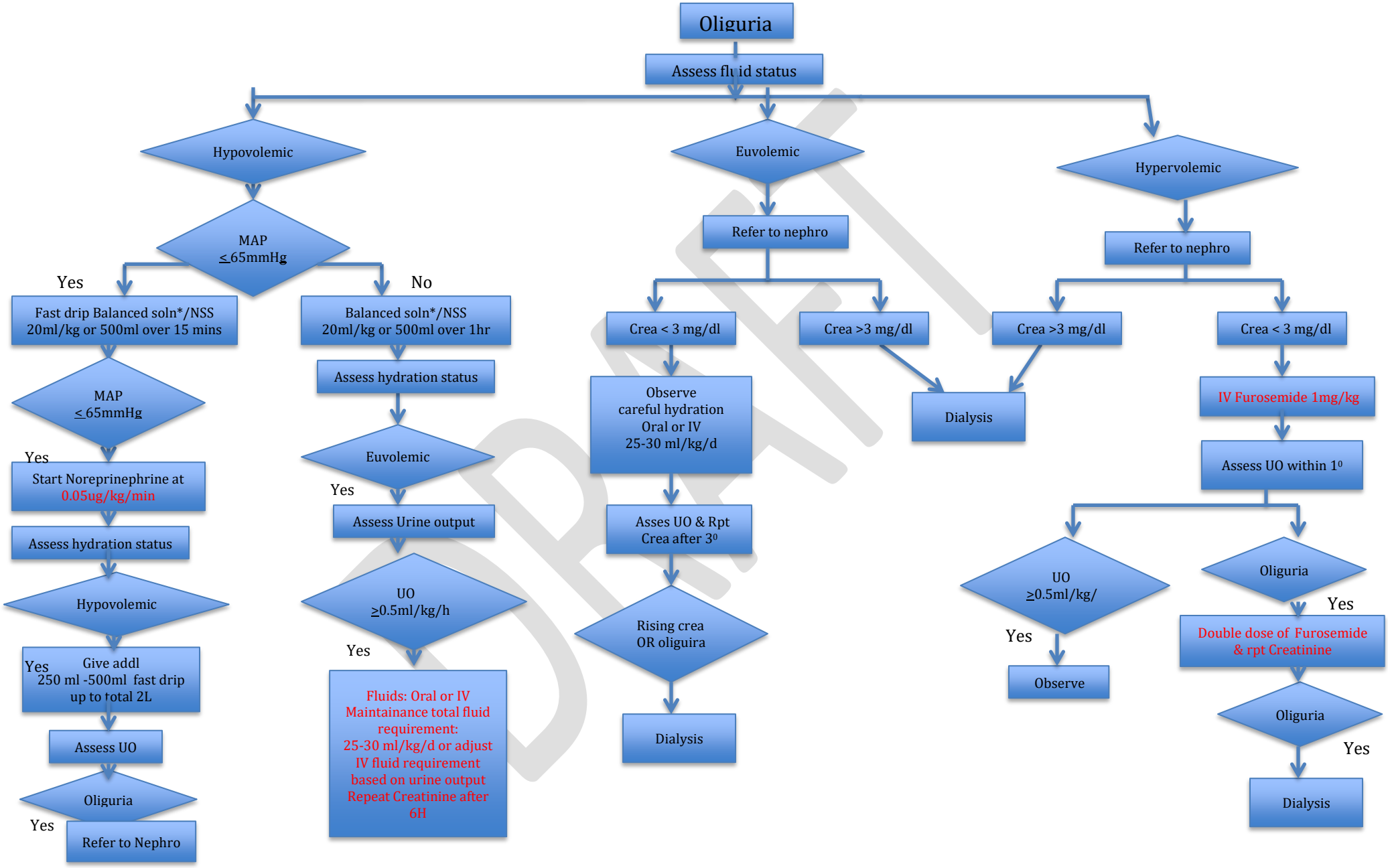
Oliguria was defined as urinary volume below 600 mL/day after hydration. When the patient remained oliguric even after effective hydration, furosemide was used. The diuretic was sustained for a maximum of 48 hours for those patients in whom oliguria was not reversed.

EVALUATION OF PENICILLIN THERAPY IN PATIENTS WITH LEPTOSPIROSIS AND ACUTE RENAL FAILURE
Elizabeth De Francesco DAHER(1,2) & Charlys Barbosa NOGUEIRA(1) 2000

The presence of oliguria (urinary volume <500 mL/day after hydration)

Support Journal: Statement 5:
Hemodynamically, in leptospirosis, the systemic vascular resistance is decreased while renal vascular resis- tance is increased,[9] and there is relative hypovolemia. In response, plasma arginine vasopressin, angiotensin II, and aldosterone are increased, which result in decreased renal blood flow, decreased GFR, and salt and water retention.[8,9] This is similar to the findings in malaria.[10] At the clinical

level, there may be subclinical hypotension or clinical hypotension when the disease is severe.[11] A decreased response to fluid load has been observed. This trade-off is a compensatory mechanism, which can be so intense to result in acute renal failure. Changes in glomer- ular filtration rate and renal blood flow depend on the severity of the disease. Based on the presence of jaundice and impaired renal function, the disease in these patients was considered severe. Switching off the compensating mechanism by volume expansion alone can be dangerous for fluid overload because of the decreased response to water load.


Oliguria
Assess fluid status
Hypovolemic
Euvolemic
Hypervolemic
MAP ≤65mmHg
Yes
No
Fast drip Balanced soln*/NSS 20ml/kg or 500ml over 15 mins
Balanced soln*/NSS 20ml/kg or 500ml over 1hr
MAP ≤65mmHg
Yes
Start Noreprinephrine at 0.05ug/kg/min
Assess hydration status
Hypovolemic
Yes
Give addl 250 ml -500ml fast drip up to total 2L
Assess UO
Oliguria
Yes
Refer to Nephro
Assess hydration status
Euvolemic
Yes
Assess Urine output
UO ≥0.5ml/kg/h
Yes
Fluids: Oral or IV
Maintainance total fluid requirement:
25-30 ml/kg/d or adjust IV fluid requirement based on urine output
Repeat Creatinine after 6H
Refer to nephro
Crea < 3 mg/dl
Crea >3 mg/dl
Observe careful hydration Oral or IV 25-30 ml/kg/d
Asses UO & Rpt Crea after 3⁰
Rising crea OR oliguira
Dialysis
Dialysis
Refer to nephro
Crea >3 mg/dl
Crea < 3 mg/dl
IV Furosemide 1mg/kg
Assess UO within 1⁰
UO ≥0.5ml/kg/
Yes
Observe
Oliguria
Yes
Double dose of Furosemide & rpt Creatinine
Oliguria
Yes
Dialysis

Pre- dialysis Management of AKI in Leptospirosis

How should a leptospirosis patient with oliguria be managed?

- See algorithm

What is the recommended target MAP for patients with Leptospirosis in Shock?

The recommended target MAP is 65-70mmHg in all patients regardless of previous history of hypertension or heart failure.

Strong Recommendation, High quality evidence

What is the recommended initial fluid resuscitation in patients with Leptospirosis with hypovolemic?/septic shock?

The recommended initial fluid resuscitation for Leptospirosis patient is Balanced crystalloids. If potassium is in the high normal value or with hyperkalemia, Isotonic saline is recommended.

Hydroxyethyl starch should be NOT be given because it is associated with increased risk of Acute Kidney Injury, need for Renal Replacement and mortality.

Strong Recommendation, Low quality of evidence

What is the recommended initial fluid resuscitation rate in patients with Leptospirosis in Hypovolemic/Septic shock?

The recommended initial fluid resuscitation rate is 20ml/kg/h or 500ml of crystalloids with in 15- 30mins

Patients with Leptospirosis are prone to ARDS due to downregulation of the Na transport via Epithelial Sodium Channel (ENaC), NaKATPase as well as decrease in Aquaporin P5.

Strong recommendation, low quality of evidence

Levels of Evidence:

IA	Evidence from meta-analysis of randomized controlled trials
IB	Evidence from at least one randomized controlled trial
IIA	Evidence from at least one controlled study without randomization
IIB	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Grades of Recommendations:

A	Directly based on Level I evidence
B	Directly based on Level II evidence or extrapolated recommendations from Level I evidence
C	Directly based on Level III evidence or extrapolated recommendations from Level I or II evidence
D	Directly based on Level IV evidence or extrapolated recommendations from Level I, II, or III evidenc

(from Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing clinical guidelines. West J Med. 170(6):348-51, 1999 June)

GRADING EVIDENCE

Grade	**Definition**
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

What are the indications for acute renal replacement therapy or dialysis?

2010	**2019**
Any ONE of the following: • **Uremic symptoms- nausea, vomiting, altered mental status, seizure, coma** • **Serum crea >3 mg/dl** • **Serum K >5 meq in an oliguric patient** • **ARDS, pulmonary hemorrhage** • **pH <7.2**	**Any ONE of the following:** • **Uremic symptoms- nausea, vomiting, altered mental status, seizure, coma** • **pH <7.2** • **Fluid overload** • **Oliguria despite adequate hydration (GRADE: high-*KDIGO AKI*)** • **Serum crea >3 mg/dl**

• **Fluid overload** • **Oliguria despite measures following the algorithm**	• **Serum K >5 meq in an oliguric patient** • **ARDS, pulmonary hemorrhage (GRADE: moderate)**

Original Article

Factors associated with severity and mortality in patients with confirmed leptospirosis at a regional hospital in northern Taiwan

Hua-Kung Wang [a,b], Mong-Hong Lee [c], Yee-Chun Chen [d], Po-Ren Hsueh [e,d,*], Shan-Chwen Chang [d]

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CITATION

PLOS | NEGLECTED TROPICAL DISEASES A Peer-Reviewed, Open Access Journal

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PLoS Negl Trop Dis. 2016 Feb; 10(2): e0004482.
Published online 2016 Feb 25. doi: [10.1371/journal.pntd.0004482]

PMCID: PMC4767218
PMID: 26914210

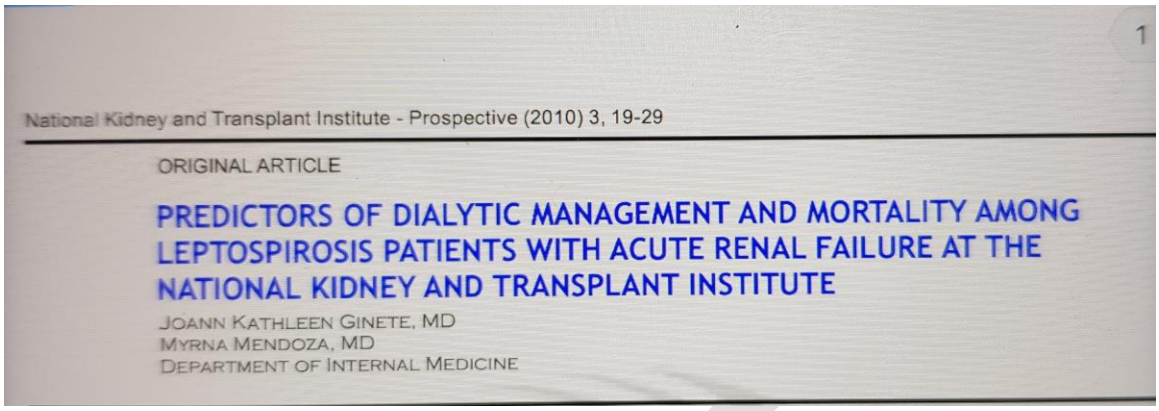
Early Indicators of Fatal Leptospirosis during the 2010 Epidemic in Puerto Rico

Tyler M. Sharp,[1,2,*] Brenda Rivera García,[3] Janice Pérez-Padilla,[2] Renee L. Galloway,[4] Marta Guerra,[4] Kyle R. Ryff,[3] Dana Haberling,[4] Sharada Ramakrishnan,[4] Sean Shadomy,[4] Dianna Blau,[5] Kay M. Tomashek,[2] and William A. Bower[4]

Joseph M. Vinetz, Editor

Abstract Go to:

Background



1

National Kidney and Transplant Institute - Prospective (2010) 3, 19-29

ORIGINAL ARTICLE

PREDICTORS OF DIALYTIC MANAGEMENT AND MORTALITY AMONG LEPTOSPIROSIS PATIENTS WITH ACUTE RENAL FAILURE AT THE NATIONAL KIDNEY AND TRANSPLANT INSTITUTE

JOANN KATHLEEN GINETE, MD
MYRNA MENDOZA, MD
DEPARTMENT OF INTERNAL MEDICINE

- Hernandez et al, 2018. **Factors associated with the Need for Renal Replacement Therapy in Leptospirosis: A Retrospective Cohort Study**

What dialysis modality should be used?

2010	**2019**
Hemodialysis (including its variants) and hemofiltration are preferred over peritoneal dialysis. The latter is a valid option if hemodialysis is not readily available.	**Hemodialysis is preferred over peritoneal dialysis in patients with AKI secondary to Leptospirosis. (GRADE: High- *KDIGO AKI*)** **The latter is a valid option if hemodialysis machine is not readily available.** **(GRADE: Low- Chang et al, CJASN, 2013, Gabriel et al, KI 2008, Nguyen et al, NEJM, 2002)**

- Hemodialysis is superior to peritoneal dialysis in the treatment of infection associated acute renal failure (Nguyen et al, NEJM, 2002)

What variant of hemodialysis would be the best option?

- There is no significant difference in terms of survival between AKI-Lepto patients who undergo conventional dialysis vs HDF (GRADE- Moderate)
- Although for hemodynamically unstable patients, CRRT is suggested (GRADE- Moderate)
- *KDIGO AKI*
- Hemodiafiltration (HDF) has benefit of reducing certain inflammatory mediators over conventional HD however mortality over time did not differ. (Cleto et al)
- There is no significant difference between SLED and SLEDf in terms of length of ICU stay, overall survival and survival time among patients with severe leptospirosis.

RESEARCH ARTICLE

Hemodiafiltration Decreases Serum Levels of Inflammatory Mediators in Severe Leptospirosis: A Prospective Study

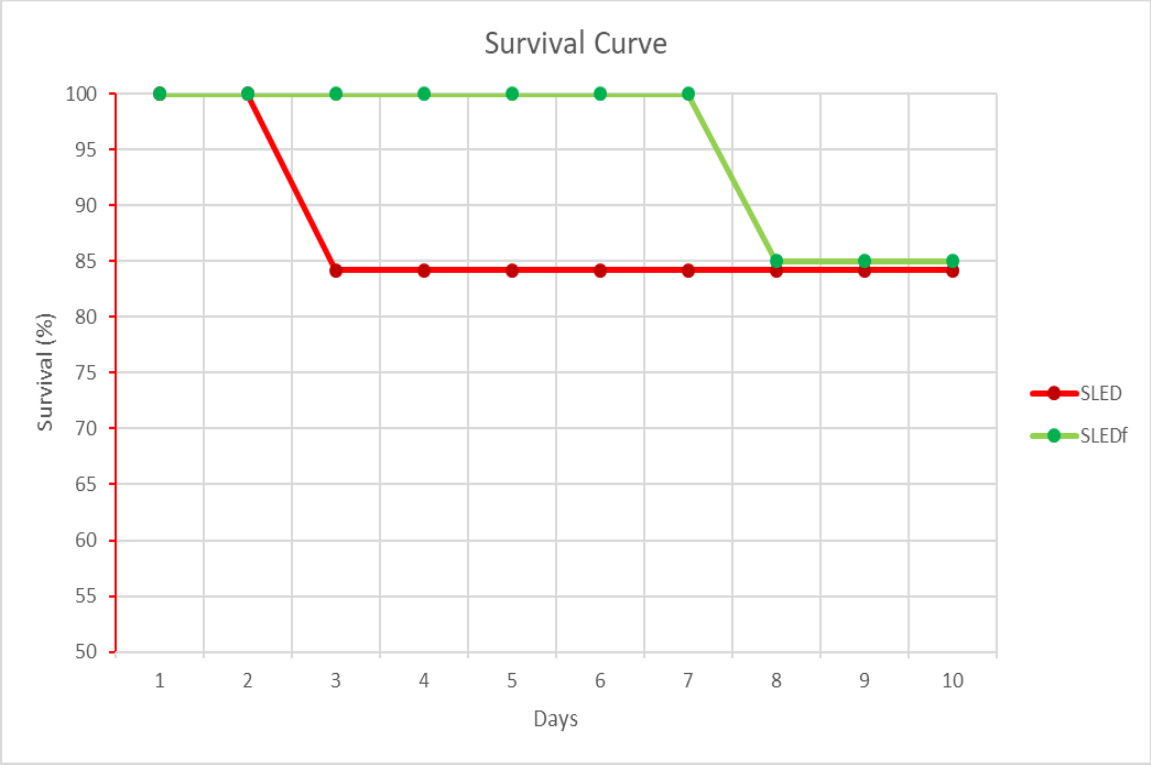
Sérgio Aparecido Cleto[1], Camila Eleutério Rodrigues[2], Ceila Maria Malaque[1], Jaques Sztajnbok[1], Antônio Carlos Seguro[2], Lúcia Andrade[2]*

1 Intensive Care Unit, Emílio Ribas Institute of Infectology, Sao Paulo, Brazil, **2** Division of Nephrology, University of Sao Paulo School of Medicine, Sao Paulo, Brazil

S2 Table Outcome measures among patients with severe leptospirosis, by the type of renal replacement therapy performed

Parameter		Type of RRT	n	Mean	Median	SD	CI	*P*
Total number of dialysis sessions		SLED	19	9.0	8.0	5.0	2.2	0.1
		SLEDf	20	12.0	12.5	7.2	3.1	
Time to recovery of renal function (days)		SLED	15	9.5	9.0	4.5	2.3	0.1
		SLEDf	17	13.0	14.0	7.0	3.3	
Time on mechanical ventilation (days)		SLED	19	9.0	9.0	4.5	2.0	0.4
		SLEDf	20	10.3	9.5	5.5	2.4	
Net fluid intake (ml/day)	Day 1	SLED	19	1.847	2.000	1.568	705	0.7
		SLEDf	20	2.074	2.000	1.697	744	
	Day 2	SLED	18	1.532	1.350	1.191	550	0.4
		SLEDf	20	1.190	1.200	1.383	606	
	Day 3	SLED	17	1.238	650	1.368	650	0.6
		SLEDf	20	971	1.465	1.761	772	
Intradialysis MAP (mmHg)	Day 1	SLED	19	76.8	74.0	15.3	6.9	0.9
		SLEDf	20	76.2	75.5	11.3	4.9	
	Day 2	SLED	19	76.8	76.0	16.8	7.6	0.4
		SLEDf	20	71.8	73.0	17.7	7.8	
	Day 3	SLED	17	83.9	82.0	13.7	6.5	0.6
		SLEDf	19	82.2	82.0	7.5	3.4	
Ultrafiltration rate (ml/dialysis session)	Day 1	SLED	19	−386	−200	920	414	0.1
		SLEDf	19	100	50	1.026	461	
	Day 2	SLED	18	−567	−630	1.296	599	0.2
		SLEDf	19	−13	100	1.160	521	
	Day 3	SLED	17	−324	−200	1.428	679	0.5
		SLEDf	16	49	210	1.536	753	
ICU stay (days)		SLED	19	17.4	16.0	10.9	4.9	0.1
		SLEDf	20	23.9	21.5	15.3	6.7	
Overall hospital stay (days)		SLED	19	23.9	23.0	13.3	6.0	0.09
		SLEDf	20	34.1	27.5	22.0	9.6	
Time to death among nonsurvivors (days)		SLED	3	3.0	2.0	2.6	3.0	0.3
		SLEDf	3	8.3	6.0	6.8	7.7	

Abbreviations: *RRT* renal replacement therapy, *SD* standard deviation, *CI* confidence interval, *SLED* sustained low-efficiency dialysis, *SLEDf* sustained low-efficiency dialysis via hemodiafiltration, *MAP* mean arterial pressure, *ICU* intensive care unit



How frequent should the dialysis be?

2010	2019
Daily dialysis should be done for critically ill patients, especially in those with pulmonary involvement	**Daily dialysis is suggested to maintain strict control of azotemia and fluid volume which can improve survival for those patients with severe Leptospirosis especially if with pulmonary hemorrhage.** • **GRADE – Moderate (KDIGO-AKI, Andrade et al, CJASN 2007, Schiffl et al, NEJM 2002)**

- Intensive Hemodialysis reduces mortality without increasing hemodynamically induced morbidity. (Schiffl et al, NEJM 2002)
- For patients with severe Leptospirosis with AKI and ARDS, shorter door-to-dialysis and daily dialysis decreases fatal complications. (Andrade et al, CJASN 2007)

- Cleto et al. Hemodiafiltration Decreases Serum Levels of Inflammatory Mediators in Severe Leptospirosis: A Prospective Study, August 3, 2016

- Andrade et al, Door-to-dialysis Time and Daily Hemodialysis in Patients with Leptospirosis: Impact on Mortality
- Schiffl et al, Daily Hemodialysis and the Outcome of Acute Renal Failure, NEJM 2002

What are the predictors of mortality for patients diagnosed with leptospirosis?

- For adults: (GRADE: Low)

A. Initial creatinine level of $\geq$ 2.2 mg/dl
   OR 2.09 p value: 0.006

B. Presence of concomitant Chronic lung Disease(CLD)
   OR 6.83 p value 0.0165

C. Presence of DM
   OR 6 p value: 0.0371

D. Hemorrhage
   OR 55.71 p value 0.0001
   - Hemorrhagic complications is defined subconjunctival suffusions, epistaxis, hematuria, hemoptysis, gastrointestinal bleeding or hematemesis

E. Arrhythmia
   OR 4.93 p value 0.0274

F. Shock
   OR 20.67 p value 0.0006
   - Defined as systolic blood pressure below 90mmhg or MAP below 70mmHg and the requirement for vasopressors

G. Jaundice
   OR value 5.57 p value 0.0256

H. Pulmonary involvement
   OR 1 p value 0.0005
   - Defined as interstitial or alveolar infiltration on chest radiography.

I. need for HD
   OR 16.88 p value 0.0201

J. need for ventilation
   OR 18.5 p value 0.0002

Original Article

Factors associated with severity and mortality in patients with confirmed leptospirosis at a regional hospital in northern Taiwan

Hua-Kung Wang [a,b], Mong-Hong Lee [c], Yee-Chun Chen [d], Po-Ren Hsueh [e,d,*], Shan-Chwen Chang [d]

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[e] *Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*

Table 2 Comparison of laboratory data of patients with severe and non-severe leptospirosis. Each value is mean ± SD or n (%).

Parameter (reference range)	All cases (n = 57)	Severe cases (n = 37)	Non-severe cases (n = 20)	*p* value[a]
Laboratory data, mean ± SD				
WBC, $10^3/\mu L$ (3.5–11)	11.62 ± 6.28	12.60 ± 7.07	9.80 ± 4.03	0.057
Platelets, $10^3/\mu L$ (150–400)	197.55 ± 94.40	214.24 ± 106.01	165.05 ± 55.38	**0.021**
Hemoglobin, g/dL (12–17)	12.33 ± 2.35	12.08 ± 2.47	12.77 ± 2.10	0.269
Urea nitrogen, mg/dL (8–20)	31.20 ± 27.78	35.82 ± 31.10	21.94 ± 16.74	**0.028**
Creatinine, mg/dL (0.4–1.4)	2.01 ± 1.79	2.24 ± 1.96	1.59 ± 1.38	0.145
AST, IU/L (1–38)	149.48 ± 308.10	172.56 ± 380.73	110.25 ± 102.30	0.350
ALT, IU/L (1–41)	91.84 ± 112.12	103.97 ± 137.38	72.05 ± 45.82	0.198
Total bilirubin, mg/dL (0.2–1.2)	1.60 ± 1.60	1.75 ± 1.80	1.34 ± 1.23	0.308
CPK, U/L (26–308)	272.78 ± 328.58	280.61 ± 296.35	248.44 ± 434.24	0.767
Sodium, mEq/L (135–148)	134.10 ± 19.43	132.41 ± 23.86	137.29 ± 3.48	0.222
Potassium, mEq/L (3.5–5.0)	3.93 ± 1.00	4.13 ± 1.16	3.56 ± 0.41	**0.007**
Albumin, g/dL (3.8–5.3)	2.68 ± 0.69	2.60 ± 0.75	2.87 ± 0.48	0.104
CRP, mg/dL (0.1–1.0)	15.93 ± 11.14	17.03 ± 11.86	13.90 ± 9.67	0.282
Positivity of seven main serovar, no. (%) of patients				
Shermani	42 (74%)	25 (68%)	17 (85%)	0.154
Bratislava	20 (35%)	17 (46%)	3 (15%)	**0.019**
Bataviae	6 (11%)	2 (5%)	4 (20%)	0.087
Tarassovi	6 (11%)	5 (14%)	1 (5%)	0.318
Icterohaemorrhagiae	5 (9%)	3 (8%)	2 (10%)	0.810
Caniola	4 (7%)	4 (11%)	0 (0)	0.127
Poi	4 (7%)	3 (8%)	1 (5%)	0.661

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; CRP = C-reactive protein; WBC = white blood cells.
[a] *p* values in boldface indicate significant differences (<0.05).

Table 3 Univariate analysis of factors associated with mortality.

Parameter	No.(%) of patients		*p* value[a]
	Survivors (n = 46)	Non-survivors (n = 11)	
Age, mean ± SD (y)	57.61 ± 17.61	65.27 ± 20.01	0.1504
Male, n (%)	35 (76)	7 (64)	0.8002
Smoking	23 (50)	4 (36)	0.7921
Underlying disease, n (%)			
Hypertension	10 (22)	3 (27)	0.3472
Chronic lung disease	5 (11)	5 (45)	**0.0034**
Diabetes mellitus	4 (9)	4 (36)	**0.0089**
Complications			
Concomitant infection	10 (22)	6 (55)	**0.0148**
Hemorrhage	7 (15)	10 (91)	**<0.0001**
Arrhythmia	9 (20)	6 (55)	**0.0090**
Shock	15 (33)	10 (91)	**0.0002**
Meningitis	6 (13)	0 (0)	0.8973
AKI	12 (26)	5 (45)	0.1036
Jaundice	11 (24)	7 (64)	**0.0054**
Splenomegaly	6 (13)	2 (18)	0.3297
Pulmonary involvement	20 (43)	11 (100)	**0.0004**
Need for dialysis	1 (2)	3 (27)	**0.0017**
Need for ventilation	9 (20)	9 (82)	**<0.0001**
Prior steroid use	7 (15)	8 (73)	**<0.0001**
Laboratory data, mean ± SD			
BUN, mg/dL	29.66 ± 27.21	37.50 ± 30.71	0.2185
Creatinine, mg/dL	2.06 ± 1.86	1.76 ± 1.51	0.7155
AST, IU/L	153.91 ± 329.61	132.18 ± 215.40	0.6056
ALT, IU/L	89.33 ± 115.38	100.73 ± 104.41	0.3751
Total bilirubin, mg/dL	1.66 ± 1.72	1.40 ± 1.18	0.7193
CPK, U/L	283.08 ± 374.35	248.46 ± 193.43	0.6668
WBC, $10^3/\mu L$	11.15 ± 4.81	13.58 ± 10.56	0.2278
Platelets, $10^3/\mu L$	188.73 ± 90.79	233.64 ± 104.70	0.0952
Hb g/dL	12.72 ± 2.25	10.66 ± 2.13	0.9978
Albumin, g/dL	2.82 ± 0.69	2.27 ± 0.52	0.9985
C-reactive protein, mg/dL	16.15 ± 10.93	15.02 ± 12.54	0.6086
Serovar positivity			
Shermani	37 (80)	5 (45)	0.9910
Bratislava	14 (30)	6 (55)	0.0661
Icterohaemorrhagiae	3 (7)	2 (18)	0.1097

AKI = acute kidney injury; BUN = blood urea nitrogen; Hb = hemoglobin.
[a] *p* values in boldface indicate significant differences (<0.05).

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PLoS Negl Trop Dis. 2016 Feb; 10(2): e0004482.
Published online 2016 Feb 25. doi: [10.1371/journal.pntd.0004482]

PMCID: PMC4767218
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Early Indicators of Fatal Leptospirosis during the 2010 Epidemic in Puerto Rico

Tyler M. Sharp,[1,2,*] Brenda Rivera García,[3] Janice Pérez-Padilla,[2] Renee L. Galloway,[4] Marta Guerra,[4] Kyle R. Ryff,[3] Dana Haberling,[4] Sharada Ramakrishnan,[4] Sean Shadomy,[4] Dianna Blau,[5] Kay M. Tomashek,[2] and William A. Bower[4]

Joseph M. Vinetz, Editor

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Abstract

Go to:

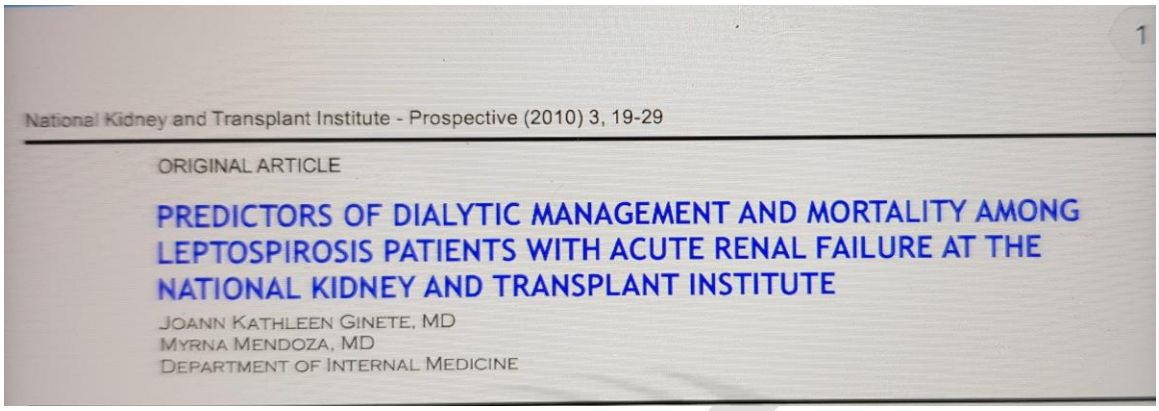
Background

S4 Table. Laboratory values and comparison results of matched fatal and non-fatal leptospirosis patients at presentation or worst recorded value during entire hospitalization, Puerto Rico, 2010.*

	At first presentation						Worst value†			
		Fatal		Non-fatal			Fatal	Non-fatal		
Variable	n	Median (Range)	n	Median (Range)	OR (95% CI)	P-value	Median (Range)	Median (Range)	OR (95% CI)	P-value
White blood cell (WBC)count (x 10^3)	21	9.9 (4.1–26.9)	52	8.4 (2.1–23.4)	1.18 (1.04–1.37)	0.006	21.7 (4.8–65.3)	13.4 (3.3–48.8)	1.1 (1.03–1.19)	0.002
Neutrophil (%)	21	89.3 (5.9–96.8)	52	79.7 (26.0–95.1)	1.04 (1.005–1.08)	0.02	90.0 (66.0–96.8)	77.4 (16.0–99.0)	1.08 (1.03–1.15)	0.0006
Platelet count (x 10^3)	21	52 (6–343)	52	56.5 (12–202)	1.01 (0.996–1.02)	0.2	21 (6–98)	34 (4–202)	0.98 (0.96–1)	0.05
Hematocrit (%)	21	37.1 (23.7–45.8)	52	40.4 (20.9–54.6)	0.94 (0.85–1.04)	0.2	26.1 (13.6–42.8)	30.2 (12.0–43.8)	0.92 (0.84–0.99)	0.03
Potassium	21	3.9 (3.0–7.0)	52	3.8 (2.8–6.0)	1.27 (0.67–2.39)	0.4	3.3 (2.6–4.3)	3.2 (2.4–5.6)	1.26 (0.51–3.14)	0.6
Bicarbonate	17	20.8 (12.9–28.0)	52	24.7 (16.3–31.0)	0.64 (0.44–0.83)	<.0001	19.2 (11.5–24.0)	21.9 (11.0–30.4)	0.79 (0.62–0.95)	0.006
Calcium	18	8.1 (6.9–9.4)	52	8.4 (6.6–9.8)	0.52 (0.23–1.12)	0.1	7.4 (6.2–8.9)	7.4 (4.3–9.1)	1.09 (0.63–1.98)	0.8
Blood urea nitrogen (BUN)	21	45.0 (3.7–168.0)	52	20.5 (5.0–78.5)	1.05 (1.01–1.09)	0.003	72.5 (11.0–173.0)	35.5 (6–242)	1.02 (1.004–1.04)	0.009
Creatinine	20	2.2 (0.9–10.3)	52	1.3 (0.6–6.0)	2.09 (1.18–4.32)	0.006	4.1 (1.0–10.3)	1.6 (0.7–13.4)	1.26 (1.01–1.64)	0.04
Albumin	14	2.4 (1.4–3.4)	47	2.8 (1.8–4.3)	0.3 (0.08–0.86)	0.02	2.0 (0.9–3.3)	2.3 (1.4–4.2)	0.43 (0.14–1.13)	0.09
Alanine transaminase (ALT)	17	111 (29–823)	48	90 (15–5,131)	1.0 (0.998–1.003)	0.5	285 (56–823)	125 (23–10,162)	1.0 (<1–1.0005)	0.6
Aspartate transaminase (AST)	16	64 (27–561)	46	77.5 (16–5614)	1.0 (0.99–1.004)	0.9	102 (36–1,350)	114 (16–5,614)	1.0 (<1–1.001)	0.7
Total bilirubin	17	7.5 (0.5–36.9)	46	1.4 (0.2–26.3)	1.17 (1.04–1.37)	0.005	14.0 (1.6–36.9)	2.8 (0.2–83.0)	1.03 (0.99–1.08)	0.2
Prothrombin time (PT)	17	12.5 (10.7–26.0)	44	13.1 (10.4–18.5)	1.15 (0.89–1.52)	0.3	13.2 (1.3–45.9)	13.2 (10.4–23.5)	1.15 (1.01–1.38)	0.03
Partial thromboplastin time (PTT)	16	31.2 (22.4–92.1)	44	29.7 (20.0–39.4)	1.08 (1.00–1.22)	0.05	32.2 (14.1–180.0)	30.3 (20.0–40.2)	1.06 (1.01–1.2)	0.005
International normalized ratio (INR)	16	1.1 (0.9–2.0)	43	1.1 (0.9–1.7)	1.4 (0.04–40.93)	0.8	1.2 (1.0–50.7)	1.1 (1.0–2.1)	4.18 (0.92–40.7)	0.07
Urine specific gravity	18	1.01 (1.00–1.03)	43	1.02 (1.01–1.03)	<0.001 (<0.001–>1000)	0.1	1.01 (1.00–1.03)	1.02 (1.01–1.03)	>1000 (<1–>1000)	0.7
Urine pH	20	6.0 (5.0–7.0)	49	5.5 (5.0–7.5)	1.26 (0.56–2.76)	0.6	5.3 (5.0–8.0)	5.5 (5.0–7.5)	1.13 (0.57–2.16)	0.8

* Only cases and controls with test results from more than one day were included.

†For WBC count, neutrophil, BUN, creatinine, ALT, AST, total bilirubin, PT, PTT, INR, and urine specific gravity, "worst" was defined by the highest valu for platelet count, hematocrit, potassium, bicarbonate, calcium, albumin, and urine pH, "worst" was defined by the lowest value.



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National Kidney and Transplant Institute - Prospective (2010) 3, 19-29

ORIGINAL ARTICLE

PREDICTORS OF DIALYTIC MANAGEMENT AND MORTALITY AMONG LEPTOSPIROSIS PATIENTS WITH ACUTE RENAL FAILURE AT THE NATIONAL KIDNEY AND TRANSPLANT INSTITUTE

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DEPARTMENT OF INTERNAL MEDICINE

Additional statements for the Lepto Algorithm

- What are the indications for pulse therapy?
  - Acute Kidney Injury PLUS Any **ONE** of the following:
    - Platelet count <100,000*
    - Mean arterial pressure (MAP) <65
      - (MAP= DBP+1/3 (SBP-DBP)
    - Requires inotropes
    - Lung infiltrates on chest xray*
    - Prolonged PT and PTT*

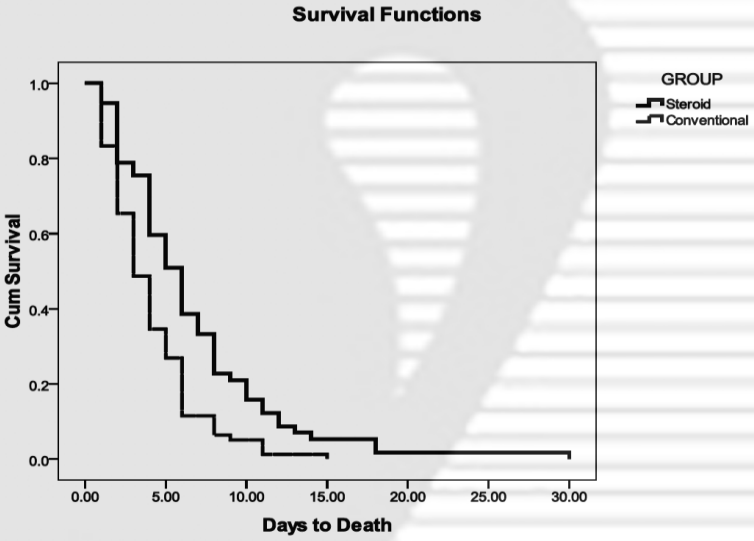
	Total n=194	Lived n=145	Died n=49	p-value
Hemoglobin (g/dL)	13 ± 2	13 ± 2	13 ± 2	0.895
WBC+ (x 10^3/uL)	15 ± 6	14 ± 6	16 ± 7	0.095
Platelet Count (x 10^3/uL)	101 ± 76	113 ± 78	64 ± 56	*<0.001
Creatinine	8 ± 3	8 ± 3	8 ± 3	0.659
PT‡ (sec)	14 ± 3	14 ± 2	15 ± 5	*0.026
PTT§ (sec)	44 ± 12	44 ± 10	47 ± 15	0.121
LAT¶				0.134
Positive	42 (22%)	29 (20%)	14 (29%)	
Negative	151 (78%)	116 (80%)	35 (71%)	
Chest Radiograph				*0.001
Clear lungs	112 (58%)	94 (65%)	18 (37%)	
Parenchymal infiltrates	82 (42%)	51 (35%)	31 (63%)	

+White blood cell count, ‡Prothrombin time, §Partial thromboplastin time, ¶Latex agglutination test

Pasamba EM, Arakama MI, Danguilan RA, Mendoza MT (2018) Outcome of Adults with Leptospirosis and Renal Failure Treated with Pulse Immunosuppression. J Kidney 4: 161. doi:10.4172/2472-1220.1000161

Hydrocortisone?

Figure2. Hazard Plot of Patients with Leptospirosis Receiving Steroids and Standard Therapy versus Standard Therapy Alone, NKTI, October – November 2009



Danguilan RA, Quilala AR, Mendoza MT, Pile M, Ninalga HD. EFFECT OF SHORT COURSE STEROID THERAPY ON THE SURVIVAL OF PATIENTS WITH SEVERE LEPTOSPIROSIS: A RETROSPECTIVE STUDY. NKTI Proceedings 2010. Unpublished

Pulse Therapy: 3 doses of Methylprednisolone plus 1 dose of Cyclophosphamide

Survival of patients among the two groups				
	Population	Hydrocortisone	Methyprednisolone+Cyclophosphamide	P value
	n=138	n=65	n=73	
Death	26 (19%)	17 (26%)	9 (12%)	0.035*
Survived	111 (81)	48 (74%)	64 (88%)	
*Statistically significant				

Why do Pulsing?

- There has been increasing evidence for an immunologic mechanism mediating renal failure and pulmonary hemorrhagic complications in leptospirosis via an exaggerated host immune response [1,2].
- Kularatne et al. in 2011 recommended early administration of methylprednisolone 500 mg IV for 3 days as it may reduce mortality in patients with severe leptospirosis except among patients with established

multiple organ dysfunction and co-morbidities (10.7% vs. 21.8% mortality rate) [3].

1. Klimpel GR, Matthias MA, Vinetz JM (2003) Leptospira interrogans activation of human peripheral blood mononuclear cells preferential
expansion of TCRγδ+ T cells vs TCRαβ+ T cells. J Immunol 171: 1447-1455.
2. Nally JE, Chantranuwat C, Wu XY, Fishbein MC, Pereira MM, et al. (2004) Alveolar septal deposition of immunoglobulin and complement
parallels pulmonary hemorrhage in a guinea pig model of severe pulmonary leptospirosis. Am J Pathol 164: 1115-1127
3 Kularatne SA, Budagoda BD, de Alwis VK, Wickramasinghe WM, Bandara JM, et al. (2011) High efficacy of bolus methylprednisolone in
severe leptospirosis a descriptive study in Sri Lanka. Postgrad Med J 87:13-17.

- Trivedi et al. in 2009 reported that addition of cyclophosphamide 60 mg/kg intravenously to standard therapy with methylprednisolone improved patient's survival from pulmonary hemorrhage (66.7% vs. 9.4% survival rate) with minor side effects (leukopenia and alopecia) [7].

Trivedi SV, Vasava AH, Patel TC, Bhatia LC (2009) Cyclophosphamide in pulmonary alveolar hemorrhage due to leptospirosis. Indian J Crit Care
Med 13: 79-84.