

Nephropathy in Leptospirosis

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ABSTRACT

Renal involvement is common in leptospirosis. Bacterial invasion, inflammatory process, haemodynamic alterations and direct toxicity of bacterial products are thought to be responsible for the development of nephropathy. Pathologically, all renal structures are involved. Interstitial nephritis is the basic lesion, and is observed even in patients without clinical renal manifestations. Tubular necrosis is the important pathological counterpart of acute renal failure. The clinical spectrum of renal manifestations includes mild urinary sediment change, hypokalemia, tubular dysfunction, decreased response to fluid load and acute renal failure (ARF). ARF reflects the severity of leptospirosis, is catabolic and is commonly associated with cholestatic jaundice. Severe renal failure may be complicated by multiple organ involvement. Renal failure with hyperbilirubinemia represents a severe form of renal dysfunction with oligo-anuria and prolonged clinical course. Mild renal failure is usually anicteric and non-oliguric and without complication. Besides antibiotic treatment, early and frequent dialysis is life saving. ARF with major organ failure has unfavorable outcome. Plasmapheresis and continuous venovenous hemofiltration improve hemodynamics and are beneficial for the patients with acute renal failure and multiorgan involvement. Recovery of renal function is usually complete in most patients.

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Leptospirosis is an infectious disease caused by *Leptospira interrogans*. A tropical environment with heavy rainfall, high humidity and wet soil is a proper media for the growth of leptospire. The causative organisms grow well in the environment with neutral or alkaline pH. Rodents, especially rats, due to their alkaline urine, are therefore an important reservoir of leptospire. Renal involvement is common in leptospirosis.^[1] This is not surprising since leptospire are highly invasive and the kidney is a highly vascular organ. Fluctuation of the pH in the renal tissue due to ammonia recycle in renal tubules and urinary acidification by hydrogen ion secretion presents a challenge to leptospire, and could increase the bacterial virulence. The kidney is, therefore, an important target organ for leptospiral infection, and nephropathy in leptospirosis is an interesting subject in medicine and microbiology.

Pathogenesis

Inflammation

Besides invasiveness of leptospire, several bacterial components including lipopolysaccharides (LPS), peptidoglycans and outer membrane proteins consisting mainly of glycolipoproteins can activate monocytes through receptors, especially CD.^[1-4] Pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF α) and interleukins are released and induce the inflammatory process through generation of several vasoactive and inflammatory mediators and adhesion molecules.^[2-6] Both Th1 and Th2 lymphocytes are involved, resulting in an immune-mediated nephropathy. Immune re-

sponse in leptospirosis is largely humoral in nature. Glomerulonephritis with deposition of IgM and C₃ in the mesangium indicates humoral mechanism. Auto-antibodies including IgG anti-cardiolipin antibodies,^[7] anti-neutrophil cytoplasmic antibodies (ANCA)^[8] and anti-platelet antibodies^[9] have been detected. Yet, the role of ANCA in the pathogenesis of vascular injury cannot be substantiated.^[10] Cell-mediated immune response through the release of cytokines and chemokines is evidenced by initial neutrophil migration to the glomeruli and interstitium. Mononuclear cells later replace the neutrophilic infiltrate. Interstitial cellular infiltration is observed within hours of leptospiral invasion.

Haemodynamic changes

As in sepsis, a number of vasoactive mediators are released in leptospirosis.^[1] Haemodynamically, systemic vascular resistance is decreased predominantly due to nitric oxide. The cardiac output and blood volume are increased. Renal vascular resistance is increased. The renal blood flow and glomerular filtration rate are decreased. Significant hypotension is observed in 60% of the patients. In a recent study, three hemodynamic patterns have been demonstrated.^[11] The first pattern observed in most patients is characterised by a decrease in systemic vascular resistance, decreased mean arterial pressure, increased cardiac index, normal pulmonary vascular resistance and pulmonary capillary wedge pressure. The second pattern, observed in the patients with pulmonary haemorrhage, shows increased pulmonary vascular resistance with normal cardiac index and systemic vascular resistance. In the third pattern, systemic vas-

cular resistance is either slightly increased or normal; the cardiac index and the mean arterial pressure are decreased; pulmonary vascular resistance and pulmonary capillary wedge pressure are normal. The patients in this group had hyperbilirubinaemia. As in other infectious diseases, there is initial hypovolaemia followed by hypovolaemia due to increased vascular permeability as the disease progresses.^[12] In cases with severe infection, the renal blood flow and glomerular filtration rate are markedly diminished to a sufficient degree to cause ARF. Non-specific inflammatory factors including haemolysis, myonecrosis, intra-vascular coagulation, free radicals, hyperbilirubinaemia and increased blood viscosity further contribute to impaired renal function.^[1]

Renal and pulmonary complications were often preceded by hypotension and prompt treatment of hypotension prevented complications.^[13] The role of hemodynamic stabilisation is under consideration. Hypotension is important, as it not only causes renal ischaemia, but it could also enhance the inflammatory process. Renal ischaemia can cause dysregulation of the lung salt and water channels. Pulmonary epithelial sodium channel (ENaC), Na-K ATPase and aquaporin-5 (AQP5) are down-regulated.^[14] Shear stress is known to regulate adhesion molecule expression, and bears a good relationship with haemodynamics.^[15-16] Alterations in haemodynamic status and shear stress could potentiate the toxicity of the outer membrane products through up-regulation of adhesion molecule expression causing more organ damage. The inflammatory process usually plays a role in ischaemic ARF.

Direct Nephrotoxicity

Leptospire are nephrophilic, and can cause renal injury by direct invasion. The alkaline pH due to ammonia generation by proximal tubules can favour bacterial growth, while acid pH is unfavourable for their survival. Fluctuations in the renal tissue pH due to ammonia recycling in renal tubules and hydrogen ion secretion with urinary acidification can be a threat to leptospire and may increase their virulence. Bacterial products, especially the outer membrane proteins consisting of OmpL1, LipL41, and LipL36 are toxic to the kidney.^[3,4,17-19] OmpL1, lipoprotein LipL41, and LPS are exposed on the surface of leptospire.^[3] The proximal tubule is the location of leptospire colonisation. Only pathogenic leptospire adhere to renal epithelial cells. In hamsters infected with a low bacterial load, LPS, OmpL1, and LipL41 were initially shown in the renal tubular lumen. They were then seen in the cytoplasm of proximal tubular cells. Later, LPS and OmpL1 were present in interstitium along with cellular infiltration. The findings suggested that these antigens were transported from the tubular lumen into the interstitium.^[3] This is in contrast to the result of a previous study using a high bacterial load, which showed the migration of leptospire from the interstitium to the tubules.^[20] The OmpL1 can adhere to the host cell membrane, activate complement, and cause cellular damage.^[17] Peptidoglycans induce polymorphonuclear leukocyte adhesion to endothelial cells, which is the basic step of inflammation.^[21] Glycolipoprotein by its incorporation with the cell membrane can cause renal tubular and vascular endothelium damage.^[22] It is also a potent inhibitor of Na-K ATPase of renal tubular

epithelial cells.^[18] The outer membrane proteins up-regulate the expression of inducible nitric oxide synthase, monocyte chemoattractant protein 1, and TNF α by the medullary thick ascending limb of Henle's loops.^[19] Nitric oxide released by the medullary thick ascending limb of Henle's loop later generates peroxynitrite, causing renal injury. Monocyte chemoattractant protein 1 accounts for the majority of monocyte chemotactic activity and plays a significant role in causing interstitial lesions.^[23] Stimulation of TNF α expression leads to nuclear factor κ B activation, which is responsible for the pathogenesis of glomerulonephritis and interstitial nephritis.^[6]

Renal Pathology

Pathologically all renal structures are involved.^[24-27] Interstitial nephritis is the basic lesion of leptospirosis. Interstitial oedema and cellular infiltration are observed, even in patients without tubular necrosis. The infiltration consists mainly of mononuclear cells and a few eosinophils. Neutrophils are present early in the course of the disease. Infiltration may be diffuse or focal around the glomeruli and blood vessels. LPS and OmpL₁ are seen in the interstitium.^[3] Interstitial haemorrhage may occur.

Glomerular changes are usually not remarkable. As in many infectious diseases, there is mesangial proliferative glomerulonephritis.^[25] Polymorphonuclear cellular infiltration may be observed in the early stages of the disease. The deposition of IgM and C3 is visible in the mesangial area and the capillary loop. Focal foot process fusion and focal thickening of the basement membrane may be observed. Focal necrotising glomerulonephritis has been reported.^[28] Yet, its specificity for leptospire renal pathology is questionable.

Vasculitis with focal haemorrhage can be observed in the acute phase of the disease,^[24] but may not be seen in the biopsied material that is usually obtained late in the course of the disease. C₃ deposition is seen in the glomerular afferent arterioles.^[20] Platelet aggregation is noted in the cortico-medullary capillaries.^[27] There is segmental necrosis of the endothelium causing interstitial haemorrhage.

Tubular changes are those of tubular necrosis, which is the common pathological counterpart of acute renal failure in leptospirosis. Tubular degeneration primarily involves the proximal tubules. Distal tubular necrosis occurs later.^[20] The outer membrane products including lipopolysaccharides and outer membrane proteins are shown in the proximal tubular lumen. Bile and heme casts may be present in the tubular lumen.

Clinical Renal Manifestations

Renal involvement may vary from sub-clinical course with mild proteinuria and urinary sediment changes to severe renal failure.^[1] The severity of the disease is largely determined by the virulence of leptospire, the bacterial load and the host defence. During the septicemic phase, erythrocytes, leukocytes and granular casts are often present. Sub-clinical myoglobinuria is detected in 67% of the patients.^[1] Hemoglobinuria is

unusual except for the patients with glucose 6 phosphate dehydrogenase deficiency and intra-vascular hemolysis.

The incidence of acute renal failure varies widely from less than 10% to over 60% of the patients depending upon the severity of the disease.^[1, 29-31] Renal failure is often hypercatabolic with rapid elevation of blood urea nitrogen and serum creatinine levels and is associated with cholestatic jaundice. Hepatocellular jaundice can be observed in patients with severe leptospirosis and profound hepatic ischaemia. Hyperbilirubinemia (total serum bilirubin over 25 mg/dl) is not uncommon. Hyperbilirubinaemic renal failure represents a severe form of renal dysfunction often with oligo-anuria. The icteric form of leptospirosis with renal failure, referred as Weil's syndrome, can be caused by a variety of serovars not necessarily associated with *L.icterohaemorrhagiae*. Renal failure reflects the severity of infection rather than infection with a specific serotype. Severe leptospirosis, therefore, is associated with a variety of complications. In a recent study, 58 patients suffering from leptospirosis-related ARF had associated haemorrhagic diathesis (80%), liver failure (72%), respiratory failure (38%), circulatory failure (33%), pancreatitis (25%) and rhabdomyolysis (5%).^[30] Hypotension is common.^[32, 33] Interestingly, in a recent outbreak of leptospirosis in Thailand, a majority of patients developed hypotension with good consciousness followed rapidly by renal failure and pulmonary complications including acute respiratory distress syndrome (ARDS), pulmonary haemorrhage and pulmonary oedema.^[33] There is a close association between impaired renal function and the plasma level of TNF α ^[33-35] with 67% of the patients with renal failure developing thrombocytopenia, and 25% to 72% of thrombocytopenic patients having impaired renal function.^[33] Yet, haemorrhagic diathesis is not common in this report.^[33] Hemolytic uremic syndrome is rare, too.^[36] Except meningism, neurological symptoms in leptospirosis are related to uremia. The duration of renal failure varies from a few days to several weeks, averaging 2 weeks. Renal function usually recovers completely within 6 months.^[30,37] Residual damage may occur in severe cases. Recovery of urinary concentration capacity may be slow.^[37]

Decreased response to fluid load

Haemodynamic status and alterations in most patients with leptospirosis are similar to those seen in subjects with sepsis. Because of systemic vasodilatation plasma aldosterone and anti-diuretic hormone levels are elevated.^[38] There is renal vasoconstriction and response to fluid load is, therefore, decreased and delayed.^[39] In this respect, fluid administration must be done with caution to avoid volume overload and pulmonary complications and prevent development of iatrogenic pulmonary oedema.

Electrolyte and acid-base abnormalities

Hypokalemia caused by kaliuresis is noted in 26%- 40% of patients with leptospirosis,^[33, 40, 41] and if it assumes alarming proportions, it leads to muscular weakness. The outer membrane proteins of leptospire inhibit Na-K ATPase.^[18] The resulting increase of intra-cellular Na decreases Na transport at the luminal border of all parts of renal tubules. Increased Na

delivery to the collecting ducts for Na-K exchange causes kaliuresis.^[42] Increased plasma aldosterone and cortisol levels further enhance K excretion. There is also evidence of inhibition of Na-K-Cl co-transport in the medullary thick ascending limb of Henle's loop.^[19,43]

Renal bicarbonate loss due to decreased proximal tubular bicarbonate reabsorption may be observed.^[44] This is attributed to proximal tubular damage, interstitial changes and Na-K ATPase inhibition. Reversible renal glycosuria, hyperphosphaturia and hyperuricosuria have been reported.^[45]

Diagnosis

Diagnosis of leptospiral nephropathy can be confused with nephropathy induced by scrub typhus, dengue haemorrhagic fever and Hanta virus infection. Bacterial sepsis also can cause ARF with multiple organ involvement. Laboratory diagnosis is, therefore, important. Although serological tests are commonly used, these tests require detectable antibodies during the second week of the disease. Culture is time consuming. Early diagnosis cannot possibly be made by serology. In this respect, detection of antigens by PCR offers early diagnosis. This is usually not readily available. Nevertheless, management can be made on the clinical grounds covering other possible diseases before laboratory diagnosis can be confirmed.

Management

Penicillin remains the drug of choice. Intravenous penicillin G is given at a dosage of 1.5 million units every 6 hours for 7 days. Although theoretically renal failure requires dose modification, because of frequent dialysis and the wide therapeutic range of penicillin, the dose usually is not adjusted. Other antibacterial agents commonly used include erythromycin, doxycycline, ceftriazone and cefotaxime. In severe leptospirosis a combination of either ceftriazone or cefotaxime and doxycycline is considered, especially when associated rickettsial infection or gram negative sepsis cannot be excluded.^[46-47]

Fluid therapy

Because of the decreased response to water load, caution must be practiced in fluid administration. Hypotension requires prompt treatment to prevent renal failure and pulmonary complications. Fluid administration along with a small dose of dopamine (2-3 mg/kg/min) corrects hypotension and increases the urine flow.^[39] Fluid overload can be avoided. Dopamine increases the renal blood flow while it decreases vascular capacitance.

Treatment of renal failure

Anicteric renal failure may spontaneously recover within a few days or one week. In general, acute renal failure in leptospirosis is hypercatabolic and requires frequent dialysis. Although haemodialysis is preferred because of the risk of bleeding due to thrombocytopenia, peritoneal dialysis is a common practice in the rural areas and is seldom complicated by bleeding. Plasmapheresis or blood exchange offers good results in patients with hyperbilirubinaemic renal failure with a total se-

rum bilirubin above 25 mg/dl.^[1,48-51]

In patients with severe leptospirosis with multiple organ failure continuous venovenous haemofiltration (CVVH) or plasmapheresis has been shown to improve systemic and renal haemodynamics and clinical condition.^[11] Nitric oxide inhalation and CVVH has been reported to be beneficial for patients with pulmonary haemorrhage.^[52] Vasopressin may be useful in patients with pulmonary complications.^[53]

Prognosis of renal failure in leptospirosis is usually favourable unless complicated by multiple organ involvement. Pulmonary complications, hyperbilirubinaemia, oligo-anuria, diarrhoea, hyperkalaemia, old age and associated infection or underlying diseases carry bad prognosis with mortality ranging from 12% to 36%.^[33, 54-57] ARF in presence of failure of two or more organ-systems carries an unfavourable prognosis.^[30]

References

- Sitprija V, Losuwanrak K, Kanjanabuch T. Leptospirosis nephropathy. *Semin Nephrol* 2003;23:42-8.
- Levett PN. Leptospirosis. *Clin Microbiol Rev*. 2001;14:296-326.
- Barnett JK, Barnett D, Bolin CA, Summers TA, Wagar EA, Cheville NF, *et al.* Expression and distribution of leptospiral outer membrane components during renal infection of hamsters. *Infect Immun* 1999;67:853-61.
- Cinco M, Vecile E, Murgia R, Dobrina P, Dobrina A. Leptospira interrogans and Leptospira peptidoglycans induce the release of tumor necrosis factor α from human monocytes. *FEMS Microbiol Lett* 1996;138:211-4.
- Haake DA. Spirochaetal lipoprotein and pathogenesis. *Microbiology* 2000;146:1491-504.
- Barnes PJ, Karin M. Nuclear factor-kappa B : A pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med* 1997;336:1066-71.
- Rugman FP, Pinn G, Palmer MF, Waite M, Hay CR. Anticardiolipin antibodies in leptospirosis. *J Clin Pathol* 1991;44:517-9.
- Constantin A, Martin F, Oksman F, Bouteiller G. Antineutrophil cytoplasmic antibodies in leptospirosis. *J Rheumatol* 1996;23:411.
- Davenport A, Rugman FP, Desmond MJ, Ganta R. Is thrombocytopenia seen in patients with leptospirosis immunological mediated? *J Clin Pathol* 1989;42:439-40.
- Abdulkader R, Sabbago E, Meireles L, Radu A. Vascular injury in acute renal failure due to leptospirosis is not associated with antineutrophil cytoplasmic antibody. *Nephron* 1993;65:156.
- Siriwanij T, Suttinont C, Tantawichien T, Chusil S, Karjanabuch T, Sitprija V. Haemodynamics in leptospirosis: Effects of plasmapheresis and continuous venovenous haemofiltration. *Nephrology* 2005;10:1-6.
- Sitprija V. Overview of tropical nephrology. *Semin Nephrol* 2003;23:3-11.
- Niwattayakul K, Homvijitkul J, Niwattayakul S, Khaw O, Sitprija V. Hypotension, renal failure and pulmonary complications in leptospirosis. *Ren Fail* 2002;24:297-305.
- Rabb H, Wang Z, Nemoto T, Hotchkiss J, Yokota N, Soleimani M. Acute renal failure leads to dysregulation of lung salt and water channels. *Kidney Int* 2003;63:600-6.
- Ando J, Tsuboi H, Korenaga R, Takada Y, Toyama-Sarimachi N, Miyasaka M, *et al.* Down-regulation of vascular adhesion molecule-1 by fluid shear stress in cultured mouse endothelial cells. *Ann N Y Acad Sci* 1995;748:148-56.
- Dore M, Simon SI, Hughes BJ, Entman ML, Smith CW. P-selectin and CD18-mediated recruitment of canine neutrophils under conditions of shear stress. *Vet Pathol* 1995;32:258-68.
- Haake DA, Champion CI, Martinich C, Shang ES, Blanco DR, Miller JN, *et al.* Molecular cloning and sequence analysis of the gene encoding OmpL₁, a transmembrane outer membrane protein of pathogenic Leptospira spp. *J Bacteriol* 1993;175:4225-34.
- Younes-Ibrahim M, Burth P, Faris MV, Buffin-Meyer B, Marsy S, Barlet-Bas C, *et al.* Inhibition of Na⁺ K ATPase by endotoxin extracted from Leptospira interrogans : A possible mechanism for the pathophysiology of leptospirosis. *CR Acad Sci III* 1995;31:619-25.
- Yang CW, Wu MS, Pan MJ, Hong JJ, Yu CC, Vandewalle A, *et al.* Leptospire outer membrane protein activates NF- κ B and downstream genes expressed in medullary thick ascending limb cells. *J Am Soc Nephrol* 2000;11:2017-26.
- Sitprija V, Pipatanagul V, Mertowidjojo K, Boonpucknavig V, Boonpucknavig S. Pathogenesis of renal disease in leptospirosis. *Kidney Int* 1980;17:827-36.
- Dobrina A, Nardon E, Vecile E, Cinco M, Patriarca P. Leptospira icterohaemorrhagiae and Leptospira peptidoglycans induce endothelial cell adhesiveness for polymorphonuclear leukocytes. *Infect Immun* 1995;63:2995-9.
- Vinh T, Adler B, Faine S. Glycolipoprotein cytotoxin from Leptospira interrogans serovar copenhageni. *J Gen Microbiol* 1986;132:111-23.
- Tang WW, Qi M, Warren JS, Van GY. Chemokine expression in experimental tubulointerstitial nephritis. *J Immunol* 1997;159:870-6.
- Arean VM. The pathologic anatomy and pathogenesis of fatal human leptospirosis (Weil's disease). *Am J Pathol* 1962;40:393-423.
- Sitprija V, Evans H. The kidney in human leptospirosis. *Am J Med* 1970;49:780-8.
- Lai KN, Aarons K, Woodroffe AJ, Clarkson AR. Renal lesion in leptospirosis. *Aust N Z J Med* 1982;12:276-9.
- De Brito T, Bohm GM, Yasuda PH. Vascular damage in acute experimental leptospirosis of the guinea pig. *J Pathol* 1979;128:177-82.
- Boonpucknavig V, Soontornniyomkij V. Pathology of renal diseases in the tropics. *Semin Nephrol* 2003;23:88-106.
- Singh SS, Vijajachari P, Sinha A. Clinic-epidemiological study of hospitalised cases of severe leptospirosis. *Indian J Med Res* 1999;109:94-9.
- Covic A, Goldsmith DJ, Gusbeth-Tatomir P, Seica A, Covic M. A retrospective 5 - year study in Moldova of acute renal failure due to leptospirosis: 58 cases and a review of the literature. *Nephrol Dial Transplant* 2003;18:1128-34.
- Cetin BD, Harmankaya O, Hasman H, Gunduz A, Otkar M, Seber E. Acute renal failure: A common manifestation of leptospirosis. *Ren Fail* 2004;26:655-61.
- Rajiv C, Manjuran RJ, Sudhayakar N, Haneef M. Cardiovascular involvement in leptospirosis. *Indian Heart J* 1996;48:691-4.
- Niwattayakul K, Homvijitkul J, Khaw O, Sitprija V. Leptospirosis in northeastern Thailand : Hypotens Comp Pub Health 2002;33:155-60.
- Tajiki MH, Salomao R. Association of plasma levels of tumor necrosis factor α with severity of disease and mortality among patients with leptospirosis. *Clin Infect Dis* 1996;23:1177-8.
- Estavojer JM, Racadot-E, Couetdic G, Leroy J, Grosperin L. Tumor necrosis factor in patients with leptospirosis. *Rev Infect Dis* 1991;13:1245-6.
- Hanvanich M, Moollaor P, Suwangoon P, Sitprija V. Hemolytic uremic syndrome in leptospirosis bataviae. *Nephron* 1985;40:230-1.
- Daher EF, Zanetta DM, Abdulkader RC. Pattern of renal function recovery after leptospirosis acute renal failure. *Nephron Clin Pract* 2004;98:8-14.
- Barsoum R, Sitprija V. Tropical nephrology. In: Schrier RW, editors. *Diseases of the kidney and urinary tract*. Lippincott Williams & Wilkins; 2001. p. 2301-49.
- Losuwanrak K, Sitprija V. Fluid administration in leptospirosis: The potential use of dopamine. *Intern Med J Thai* 2003;19:180-4.
- Seguro AC, Lomar AV, Rocha AS. Acute renal failure of leptospirosis : Nonoliguric and hypokalemic forms. *Nephron* 1990;55:146-51.
- Abdulkader RC, Seguro AC, Malheiro PS, Burdman EA, Marcondes M. Peculiar electrolytic and hormonal abnormalities in acute renal failure due to leptospirosis. *Am J Trop Med Hyg* 1996;54:1-6.
- Magaldi AJ, Yasuda PN, Kudo LH, Seguro AC, Rocha AS. Renal involvement in leptospirosis : A pathophysiological study. *Nephron* 1992;62:332-9.
- Lin CL, Wu MS, Yang CW, Huang CC. Leptospirosis associated with hypokalaemia and thick ascending limb dysfunction. *Nephrol Dial Transplant* 1999;14:193-5.
- Yang CW, Wu MS, Pan MJ. Leptospirosis renal disease. *Nephrol Dial Transplant* 2001;16:73-7.
- Liberopoulos E, Bairaktari E, Elisaf M. Reversible proximal tubular dysfunction in a patient with acute febrile illness, marked hyperbilirubinemia and normal renal function: evidence of leptospirosis. *Nephron* 2002;91:532-3.
- Suputtamongkol Y, Niwattayakul K, Suttinont C, Losuwanaluk K, Limpiboon R, Chierakul W, *et al.* An open randomized controlled trial of penicillin, doxycycline and cefotaxime in patients with severe leptospirosis. *Clin Infect Dis* 2004;39:1417-24.
- Panaphut T, Domrongkitchaiporn S, Vibhagool A, Thinkamrop B, Sussaengrat W. Ceftriaxone compared with sodium penicillin G for treatment of severe leptospirosis. *Clin Infect Dis* 2003;36:1507-13.
- Sitprija V, Chusilp S. Renal failure and hyperbilirubinemia in leptospirosis. Treatment with exchange transfusion. *Med J Aust* 1973;1:171-2.
- Pecchini F, Borghi M, Bodini U, Copercini B, Grutta d' AC, Romanini GL, *et al.* Acute renal failure from leptospirosis: New trends of treatment. *Clin Nephrol* 1982;18:164.
- Pochanugool C, Sitprija V. Hyperbilirubinemic renal failure in tropical disease: Treatment with exchange transfusion. *J Med Assoc Thai* 1978;61:75-7.
- Tse KC, Yip PS, Hui KM, Li FK, Yuen KY, Lai KN, *et al.* Potential benefit of plasma exchange in treatment of severe icteric leptospirosis complicated by acute renal failure. *Clin Diagn Lab Immunol* 2002;9:482-4.
- Borer A, Metz I, Gilad J, Riesenberk K, Weksler N, Weber G, *et al.* Massive pulmonary haemorrhage caused by leptospirosis successfully treated with nitric oxide inhalation and haemofiltration. *J Infect* 1999;38:42-5.
- Laurent PO, Laurent R, Veronique B, Bernard L. Desmopressin therapy for massive hemoptysis associated with severe leptospirosis. *Am J Respir Crit Care Med* 2003;167:726-8.
- Daher E, Zanetta DM, Cavacante MB, Abdulkader RC. Risk factors for death and changing patterns in leptospirosis acute renal failure. *Am J Trop Med Hyg* 1999;61:630-4.
- Marotto PCF, Nascimento CM, Eluf-Neto J, Marotto MS, Andrade L, Sztajnbock J, *et al.* Acute lung injury in leptospirosis: Clinical and laboratory features outcome, and factors associated with mortality. *Clin Infect Dis* 1999;29:1561-

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56. Perrocheau A, Perolat P. Epidemiology of leptospirosis in New Caledonia (South Pacific): A one-year survey. *Eur J Epidemiol* 1997;13:161-7.
57. Trevejo RT, Rigau-Perez JG, Ashford DA, McClure EM, Jarquin-Gonzalez C, Amador JJ, *et al*. Epidemic leptospirosis associated with pulmonary hemorrhage-Nicaragua. 1995. *J Infect Dis* 1998;178:1457-63.