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PATHOGENESIS OF LEPTOSPIROSIS-ASSOCIATED ACUTE KIDNEY INJURY

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ABSTRACT

Leptospirosis is a disease caused by *Leptospira*, a genus from spirochaetes bacteria. It is transmitted to human through direct contact with contaminated water or soil by vector's urine. About 10% cases can develop to severe forms including acute respiratory distress syndrome, pulmonary edema, hepatic failure, and acute kidney injury (AKI). The pathogenesis of leptospirosis-associated AKI including, direct effect of *Leptospira*, tubular alterations, prerenal AKI, hyperbilirubinemia, and rhabdomyolisis. Clinical manifestations in AKI of leptospirosis are characterized by the absence of oliguria and normal or reduced potassium serum.

KEYWORDS: *Leptospira*, Leptospirosis, Pathogenesis, Acute Kidney Injury.

INTRODUCTION

Leptospirosis is a disease caused by *Leptospira*, a genus from spirochaetes bacteria.[1] The common vectors of *Leptospira* i.e rodents, pigs, dogs, cattle, horses. Leptospirosis is transmitted to human through direct contact between abrased skin or mucosal membranes with water or soil that are contaminated by vector's urine.[2] The risk groups of leptospirosis i.e sewage workers, farmers, military personnel, or individuals partaking in water sports and recreation. Leptospirosis is commonly cause epidemics in tropical country after heavy rainfall or flooding.[3,4]

Clinical manifestations of leptospirosis such as flu-like symptoms (headache, chills, fever) are spontaneously resolve in 90% cases. However, 10% cases develop to severe forms that lead to death.[1] A systematic review estimate a worldwide annualy case of leptospirosis is 1.03 million cases ($CI_{95\%}$ 434,000-1,750,000) and 58,900 deaths due to leptospirosis.[3]

Severe forms of leptospirosis is known as Weil's syndrome a multisystem damage including acute respiratory distress syndrome, pulmonary edema, hepatic failure, and acute kidney injury (AKI).[1,2,5]

In some countries in Southeastern Asia (such as Thailand and Singapore), leptospirosis is the etiology in 20% cases of AKI. AKI is a result of nephritis induced by leptospirosis. Moreover, hemodynamic alteration in leptospirosis can lead a pre-renal AKI.[6,7] This review is summarized the immune response in severe leptospirosis; pathogenesis and clinical manifestations of AKI due to leptospirosis.

IMMUNE RESPONSE IN SEVERE LEPTOSPIROSIS

Pattern Recognition Receptors (PRRs), mainly Toll-like receptors (TLRs), are expressed at the surface of innate immune cells after contact with Microbial Pathogen-Associated Molecular Patterns (PAMPs). This activates intracellular signaling pathways, i.e nuclear factor kβ (NF-kβ) and activator protein 1 (AP-1) transcription factors. These two factors regulate the expression of Prostaglandins (PGs) and Nitric Oxide (NO) that increase arterial dilation and vascular permeability.[1]

NF-kβ and AP-1 were also regulate the expression of other pro-inflammatory cytokines, i.e interleukins (IL)-1β, IL-6, IL-12, interferons (IFNs) and tumor necrosis factors (TNFs). These cytokines recruit the leucocytes to the site of infection. Severe leptospirosis associate with prolonged increase of IL-1β, IL-6, and TNF-α that lead to persistent inflammation and massive production of cytokines. Consequently, the impairment of local organ perfusion is occur, as a result of tissue edema, and lead to a loss organ function.[1]

PATHOGENESIS LEPTOSPIROSIS-ASSOCIATED AKI

DIRECT EFFECT OF *LEPTOSPIRA*

Leptospira penetrate the tissue barriers via abrasion skin and mucosal membrane of the conjunctivae or oral cavity. The bacteria disseminate systemically and persist in the bloodstream for the first eight day of fever.[4] *Leptospira* adheres to cadherin, a type of cell adhesion molecule in vascular endothelium, and migrate from bloodstream into tissue.[5,6] This bacteria can be identified in renal tubules after the first 7 days.[7]

Leptospira adhere to the epithelial surface of renal tubules. The antigenic components (i.e endotoxins, lipoproteins, lipopolysaccharides, and peptidoglycans) of the outer membrane of

leptospira lead to tubular dysfunction and inflammation.[7] The most important outer membrane protein (OMP) of *Leptospira* that expressed during infetion is LipL32. This OMP binds to toll like receptor (TLR2) in proximal tubule and activate transcription NF-kβ. NF-kβ increase the expression of pro-inflammatory proteins, i.e inducible nitric oxide synthase (iNOS) and tumor necrosis factor (TNF-α). NF-kβ also stimulate the production of monocyte chemotactic protein-1 (CCL2/MCP-1) that recruite the inflammatory cells lead to tubulointerstitial nephritis (figure 1).[7]

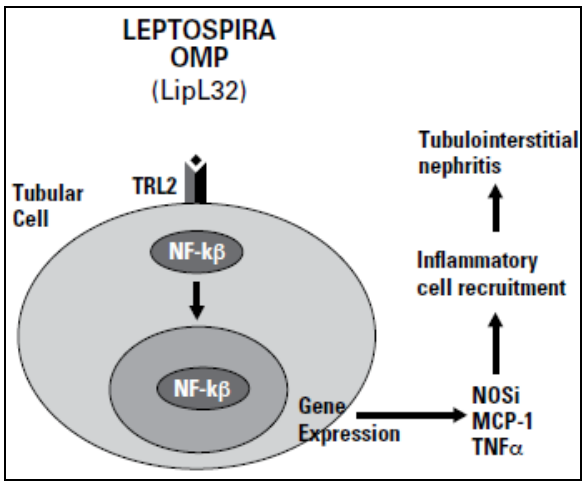

Figure 1: Direct Effect of Leptospira in Renal Tubule[7] (OMP: Outer Membrane Protein; TLR2: Toll Like Receptor; iNOS: inducible Nitric Oxide Synthase; MCP-1: Monocyte Chemotactic Protein-1; TNF-α: Tumor Necrosis Factor-α)

Tubular Alterations

The experimental study in animal with leptospirosis showed an increase in the expression of the Na^+K^+2Cl cotransporter (NKCC2). NKCC2 is one of the proteins with highest sodium reabsorption capacity in the renal tubule. A subtle changes of NKCC2 will alter the sodium reabsorption process.[8] Leptospirosis also cause resistance of vasopressin in collecting tubule that lead to polyuria.[7]

Prerenal Aki

Leptospira infection can cause fever, diarrhea, and vomiting that reduce the blood plasma volume and lead to hypotension.[9] Moreover, leptospirosis reduce sodium reabsorption in the proximal tubule so that induce hypotension. Hypotension reduce blood flow into renal and lead to an acute tubular necrosis (ATN).[7]

Hyperbilirubinemia and Rhabdomyolisis

Hyperbilirubinemia are common in leptospirosis. A study by Sitprija *et al* report a reduction in renal blood flow and creatinine clearance in patients with serum bilirubin 30,5 to 40,1 mg/dL. There is also inhibition of sodium reabsorption in the thick ascending limb of Henle's loop in patients with hyperbilirubinemia. Rhabdomyolisis has been reported in 45% to 62% of leptospirosis cases. Rhabdomyolisis lead to increase of myoglobin level in blood. Myoglobin cause direct toxicity to kidney, tubular obstruction, and renal vasoconstriction.[7]

Clinical Manifestations

Clinical manifestations of AKI caused by leptospirosis are different with AKI of other infectious causes. There is an absence of oliguria and normal or reduced potassium serum in AKI of leptospirosis. This characterstics can be observed in 41% to 45% patients with AKI of leptospirosis. The result of a study in 20 leptospirosis patients show the presence of proteinuria in all patients. Tubular dysfunction cause alterations, i.e glycosuria, reduced phospate reabsorption, bicarbonaturia, and hypermagnesuria.[2,7] Another characteristic of AKI from ultrasound finding is enlarged kidney indicating tubulointerstitial nephritis. This is a reversible process which means the kidney can recover into its normal size.[7]

Treatment

Hypotension in AKI need an appropriate hydration. AKI caused by leptospirosis need an intensive care including possibility of dialysis. A study in 33 patients with leptospirosis show a significant reduction in mortality in patients undergoing early dialysis compared late dialysis (16.7% vs 66.7%). Leptospirosis also require an early antibiotic therapy. Antibiotics that be recommended by World Health Organization (WHO) 2003, i.e intravenous benzylpenicillin (30 mg/kg up to 1.2 g 6-hourly for 5-7 days); ceftriaxone (1 g/day); or cefotaxime (1 g every 6 hours).[4,7]

CONCLUSION

AKI in *Leptospira* infection can occur by direct effect of *Leptospira* to renal tubule, hemodynamic alteration, hyperbilirubinemia, and rhabdomyolisis. The characteristics of AKI in leptospirosis are absence of oliguria and normal or reduced potassium serum.

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