RENAL DYSFUNCTION IN DENGUE VIRUS INFECTION

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Abstract. Dengue virus infection can exhibit a wide spectrum of renal dysfunction including tubular dysfunction (dyskalemia, dysnatremia, and acute tubular necrosis), and less commonly glomerular injury (*ie* microscopic hematuria or sub-nephrotic to nephrotic range proteinuria). Data from previous reports have shown that the incidence could be up to 80%. The pathogenesis of dengue-associated renal dysfunction is still unclear. Proposed mechanisms include two major effects: direct effect and indirect effect such as hemodynamic factor and immunologic factor. Until the present time, supportive treatment is still the only key treatment in dengue-associated renal dysfunction. This narrative review aims to discuss current evidences regarding the epidemiology, pathogenesis, and various renal manifestations in dengue virus infection.

Keywords: denque infection, renal dysfunction, glomerular injury

INTRODUCTION

Dengue virus infection is one of the most significant human viral mosquito-borne infections. The main pathogen is dengue virus, an RNA *Flavivirus,* which comprises of four serotypes, DEN-1 to DEN-4. The female *Aedes aegypti* is the main vector. Once infection occurs with one serotype, there will be lifelong protection to that serotype but only a few-month protection for the remaining serotypes (Gibbons and Vaughn, 2002; Guzman and Kuri, 2002).

Dengue has an incubation period of 3-14 days and will replicate in reticuloendothelial system during this phase. The clinical spectrum ranges from asymptomatic (as many as 50% of individual infections), dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), which is the most severe form of dengue infection.

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Renal involvement is one of the most significant target organ involvements in dengue infection. Acute kidney injury (AKI) has been increasingly recognized in dengue virus infection. The incidence of AKI was once as low as 1.6% among 617 Colombian children with dengue virus infection (Mendez and Gonzalez, 2003), but in the recent report, the incidence of AKI had risen to as high as 35.7% in adults infected by dengue virus admitted to the tertiary hospital in India (Basu *et al,* 2011). Most cases of patients who developed AKI were related to hypotension (42.9%), rhabdomyolysis (21.4%), and hemolysis (7.1%), carrying an increased risk of death (Lima *et al,* 2007). Microscopic hematuria and proteinuria could be detected in up to 12.5% and 80% of patients with DHF, respectively (Futrakul *et al,* 1973). Lastly, evidence from a few reports with available renal biopsy demonstrated the glomerular involvement and hemolytic uremic syndrome in patients with dengue virus infection (Wiersinga *et al,* 2006).

EPIDEMIOLOGY AND RISK FACTORS

The prevalence of AKI in previous studies has varied widely due to heterogeneous criteria of AKI used, differing populations, and differing severities of dengue virus infection in those studies. Current available data were mainly derived from

case reports and retrospective studies. Two studies used an elevation of serum creatinine of at least 2 mg/dl for the definition of AKI, and these studies may have underestimated the prevalence of AKI (Laoprasopwattana *et al,* 2010; Lee *et al,* 2009). However, later studies have applied the Acute Kidney Injury Network (AKIN) criteria and the risk, injury, failure, loss of kidney function, and end-stage acute kidney disease (RIFLE) criteria, both of which have allowed for more diagnoses of AKI (Kuo *et al,* 2008; Basu *et al,* 2011; Khalil *et al,* 2012; Mehra *et al,* 2012; Khan *et al,* 2014; Mallhi *et al,* 2015). Table 1 shows the prevalence of AKI, ranging from 0.2% to 35.7%. There is higher proportion of AKI in earlier stages. Mallhi *et al* (2016) used the conventional definition (serum creatinine ≥ 2 mg/dl), RIFLE, and AKIN criteria for diagnosis of AKI in dengue, and showed the incidence of AKI to be 4.2%, 12.6%, and 14.6%, respectively. The AKIN and RIFLE criteria were comparable while the conventional definition was the least sensitive criteria and might miss earlier stage of AKI (Mallhi *et al,* 2016).

Risk factors for dengue-associated AKI have been previously reported in the literatures. In a retrospective study of 304 hospitalized patients with DHF in Taiwan where AKI developed in 10 patients (3.3%) (Lee *et al,* 2009), the multivariable logistic regression was performed using various clinical and laboratory factors including age, gender, history of stroke, chronic kidney disease, concurrent gastrointestinal bleeding, concurrent bacterial infection, hemoglobin, activated partial thromboplastin time, and development of DSS, all of which showed significant difference between DHF patients with and without AKI. The result revealed that only DSS was the independent risk factor for development of AKI [odds ratio (OR) = 220; 95% CI: 19.8-2443.9; $p<0.001$]. However, the study had major limitation due to small number of AKI patients for the multivariate analysis. In the adjusted model there was almost 10 variables using in the model. This limitation made the disputable results. Another retrospective study in Pakistan reviewed 532 adult patients with dengue virus infection, 71 of which developed AKI (13.3%) (Khalil *et al,* 2012). After multivariable logistic regression, the independent predictors of AKI were male gender (OR=4.43; 95%CI: 1.92-10.23; $p<0.001$), development of DHF or DSS (OR=2.14; 95%CI: 1.06-4.32; $p=0.03$), neurological involvement (OR=12.08; 95%CI: 2.82-51.77; $p=0.001$), and prolonged aPTT (OR= 1.81; 95%CI: 1.003-3.26; $p=0.04$). Recently, in a study of 667 dengue patients in Malaysia in which AKI were diagnosed in 95 patients (14.2%) by AKIN criteria, multivariable logistic regression disclosed that presence of DHF (OR=8.0; 95% CI:3.64-17.59; $p<0.001$), rhabdomyolysis (OR=7.9; 95%CI: 3.04-20.49; $p<0.001$), multiple organ dysfunction (OR=17.19; 95%CI: 9.14-35.12; $p<0.001$), diabetes (OR=4.7; 95% CI: 1.12-19.86; $p=0.034$), late hospitalization (OR=2.1; 95% CI: 1.06-4.13; $p=0.033$), and use of nephrotoxic drugs (OR=2.9; 95% CI: 1.34-6.11; $p=0.006$) were independent risk factors for AKI (Mallhi *et al,* 2015).

CLINICAL MANIFESTATION AND PATHOGENESIS

Dengue-associated AKI

Clinical and pathological data concerning the histopathology of AKI in dengue virus-infected patients is limited. From these limited data, the histopathology of AKI in dengue virus infection patients comprises of acute tubular necrosis (ATN), glomerulopathy, and rarely thrombotic microangiopathy. Hemodynamic instability, which results from plasma leakage syndrome, plays a major role in the pathogenesis of AKI. Other mechanisms have also been proposed including rhabdomyolysis or hemolysis leading to ATN and acute glomerular injury (Oliveira and Burdmann, 2015) (Fig 1 and Fig 2).

Hemodynamic factors. Patients with severe dengue virus infection, mostly in secondary infection, develop plasma leakage syndrome resulting in clinical signs of hemodynamic instability including hemoconcentration, tachycardia, narrow pulse pressure, and eventually hypotension. This process is believed to result from inflammatory cytokines particularly tumor necrosis factor

Table 1. Summary prevalence of acute kidney injury (AKI) and mortality.

Author	Year	Country	No.	Age (yrs)	Severity of dengue	Definition of AKI	AKI (%)	Mortality of AKI *vs* non-AKI (%)
Mendez and Gonzalez	2003	Columbia	617	<13	DHF	NR	1.6	NR
Khan *et al*	2008	Saudi Arabia	91	6-94	DHF	NR	2.2	NR
Kuo *et al*	2008	Taiwan	519	>18	DF/DHF/DSS	RIFLE	9.3	28.6 *vs* 1.2
							I 79.7	
							II 10.8	
							III 9.5	
Lee *et al*	2009	Taiwan	304	>18	DHF/DSS	Cr > 2 mg/dL	3.3	60 *vs* 0
Laoprasopwattana *et al*	2010	Thailand	2,893	<15	DF/DHF/DSS	Cr > 2 mg/dL	0.9	64 *vs* 0
Bhaskar *et al*	2010	India	128	>18	DHF	NR	12	NR[a]
Bunnag *et al*	2011	Thailand	50	<15	DSS	NR	10	NR
Basu *et al*	2011	India	28	>18	NR	RIFLE	35.7	60 *vs* 5.6
Mehra *et al*	2012	India	223	>18	DF/DHF	AKIN	10.8	NR[b]
							I 50	
							II 29.2	
							III 20.8	
Lumbiganon *et al*	2012	Thailand	99	<18	Fatal DF	NR	25.0	NR
					Fatal DHF		14.3	
Khalil *et al*	2012	Pakistan	532	>18	DF/DHF/DSS	AKIN	13.3	11.3 *vs* 0
							I 64.8	
							II 18.3	
							III 16.9	
Khan *et al*	2014	Malaysia	124	>18	DHF	AKIN	7.2	NR
							I 22	
							II 78	
Vachvanichsanong *et al*	2015	Thailand	2,221	<15	DF/DHF/DSS	NR	0.2	NR
Mallhi *et al*	2015	Malaysia	667	>18	DF/DHF/DSS	AKIN	14.2	8.4 *vs* 0
							I 76.8	
							II 16.8	
							III 6.4	

DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; AKI, acute kidney injury; NR, not reported; Cr, creatinine; I, AKIN stage 1; II, AKIN stage 2; III, AKIN stage 3.

[a]Overall mortality was 14%, but comparison between patients with and without AKI was not reported.

[b]Mortality was significantly higher in patients with AKI ($p < 0.01$) but the exact proportion was not described in the literature.

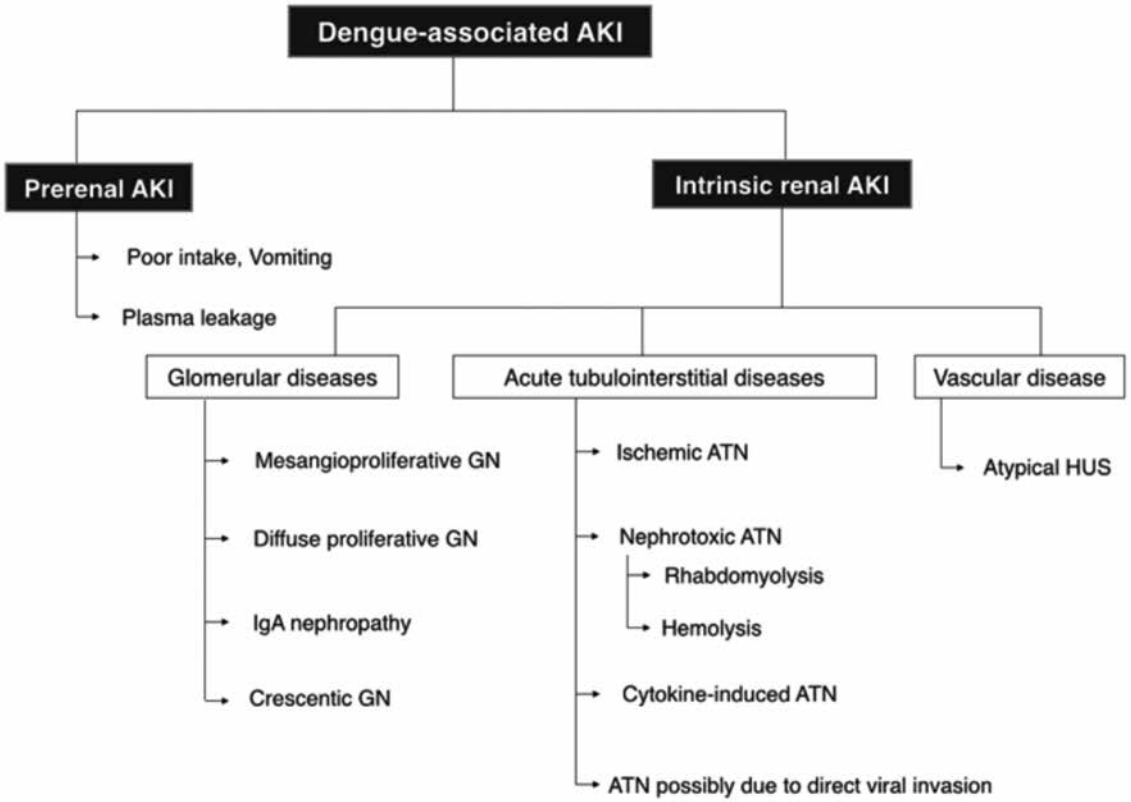

Fig 1- Clinical approach to dengue associated AKI. Abbreviation: DVI, dengue virus infection; AKI, acute kidney injury; ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, haemolytic uremic syndrome.

alpha (TNF-α), interleukin (IL)-6, IL-17, and IL-18, all of which are produced by dengue-infected monocytes (Anderson *et al,* 1997; Pagliari *et al,* 2016) and mast cells (Brown *et al,* 2011). Such changes lead to renal hypoperfusion and AKI. A retrospective study of 532 patients with dengue virus infection, in which AKI developed in 71 patients (13.3%), found that the presence of DHF or DSS was an independent predictor of AKI (OR=2.14; 95%CI: 1.06-4.32, $p = 0.03$), thus confirming the significance of hemodynamic factors in the development of AKI (Khalil *et al,* 2012). The pattern of AKI in this regard is likely ATN although kidney biopsy has not been performed generally.

Rhabdomyolysis and hemolysis. Rhabdomyolysis rarely occurs in dengue virus infection and the underlying pathogenesis of dengue-induced muscle injury has not been established (Huang *et al,* 2015). Direct invasion by the virus is a possibility suggested by identification of the viral particle by electron microscopy in the thigh muscles of dengue-infected mice (Nath *et al,* 1982). On the other hand, inflammatory cytokines can be myotoxic, especially TNF-α, causing injury to the muscles (Gandini *et al,* 2011). Rhabdomyolysis causes AKI by multiple mechanisms. Firstly, muscle injury leads to fluid sequestration into the damaged muscles, followed by intravascular volume depletion. The subsequent reduction in renal blood flow results in activation of a neuroendocrine homeostatic response as well as the release of vasoactive mediators, including endothelin-1, thromboxane A2, and TNF-α, which eventually promotes intrarenal vasoconstriction and AKI. Secondly, direct tubular damage can be caused

by myoglobin, which is excessively produced and freely filtered through the glomerular filtration slits. Lastly, myoglobinuria can also cause intratubular obstruction by forming casts in the tubular lumen (Bosch *et al,* 2009).

Reported cases of dengue virus infection, rhabdomyolysis, and AKI are available. Serum creatine phosphate kinase level ranged from 4,063 to 156,900 IU/l, and most patients were oliguric at diagnosis (Repizo *et al,* 2014). Repizo and colleagues also performed renal biopsy in a 28-year-old Brazilian man presented with DF, rhabdomyolysis, and non-recovery AKI, showing acute tubular necrosis. Immunohistochemistry for myoglobin was positive in the renal tubules suggesting that ATN might be contributed, in part, by deposition of toxic myoglobin (Repizo *et al,* 2014).

Direct viral invasion. Data from autopsies of fatal dengue virus infection cases demonstrated the presence of dengue virus in the skin, liver, spleen, lymph node, bone marrow, lung, brain, and kidney, which indicates the possibility of direct cytopathic effects of dengue virus on renal tissues (Martina *et al,* 2009). Data from animal studies provide insight in this issue. Kidneys obtained from mice transfected with human DEN-2 for 48 hours revealed diffuse increase in glomerular volume, mesangial and endocapillary hypercellularity, and immunoglobulin (Ig) M deposition in the glomeruli (Barreto *et al,* 2004). The viruses were also detected after inoculation of mouse renal tissue into mosquito cell cultures using an electron microscopy and immunofluorescence technique, thus confirming the presence of viral particle in affected organs. Unfortunately, detailed localization of dengue virus in the tissue could not be attained.

Similar findings were also reported in humans. Renal biopsies in 12 of 20 dengue patients with renal disease detected dense spherical particles of 40-50 nm in diameter in the monocyte-like cells infiltrating the glomeruli (Boonpucknavig *et al,* 1976). Further localization of the dengue antigen was conducted on renal tissues from dengue patients by using immunohistochemistry (IHC) demonstrating viral antigens only within the tubular cells (Jessie *et al,* 2004). However, *in situ* hybridization (ISH) was also performed in the same study to detect positive-strand dengue virus RNA. In contrast to the IHC result, ISH did not detect dengue virus RNA in the renal tubular cells, but only observed dengue virus RNA in the spleen and blood-clot leukocytes. These findings imply a lack of viral replication in the renal tissues, which is against the pathogenic hypothesis of direct viral invasion.

A rare model of possible direct viral invasion and AKI is dengue-induced hemolytic uremic syndrome. This condition has only been reported in three patients to date (Wiersinga *et al,* 2006; Boyer and Niaudet, 2011). The first reported case presented with DF, malignant hypertension, and microangiopathic hemolytic anemia. Renal biopsy showed glomerular and arteriolar microthrombi consistent with acute thrombotic microangiopathy. Electron microscopy also revealed microtubulo-reticular structures in vascular endothelial cells, suggesting a process of viral infection (Wiersinga *et al,* 2006).

Immune response. Host immune response may be involved in the pathogenesis of dengue associated AKI. The concept of secondary infection as the key pathogenic factor for developing DHF/DSS has been well established for decades. Once infected with dengue virus, a human develops life-long antibodies to that particular serotype while antibodies to other serotypes only last for a few months. When the patient gets infected by another strain of dengue virus, a severe inflammatory response ensues, causing DHF or DSS (Whitehorn and Simmons, 2011). This phenomenon is explained by antibody-dependent enhancement (ADE). A previous infection by one serotype of dengue virus results in development of subneutralizing antibodies. These antibodies possess high viral attachment efficiency, enhancing internalization of virus into cells through FCγ receptor (FCγR)-dependent or FCγR-independent mechanisms. The FCγR-dependent mechanism is also proposed to suppress type I interferon-

mediated antiviral responses and promotes the T-helper-2 response, whose antiviral effect is less than the T-helper-1. Eventually, ADE enhances viral replication and cytokine or chemokine production, leading to cytokine-mediated endothelial activation mainly by TNF-α and plasma leakage syndrome (Wan *et al,* 2013).

Support for the role of the immunologic mechanism in the pathogenesis of dengue-associated AKI is based on a report of DHF patients who developed AKI in the absence of hypotension, hemolysis, and rhabdomyolysis (Lima *et al,* 2007). These observations raise the possibility of direct viral invasion as well as immune-mediated mechanisms. As previously mentioned, one series of DHF cases from Thailand reported albuminuria, hematuria, and low complement factor 3 (C_3) in 71%, 12.5%, and 82%, respectively, together with azotemia, which suggested immune-complex-mediated acute glomerular disease (Futrakul *et al,* 1973). There were reports of DHF and AKI associated with proteinuria, hematuria, and reduced serum C_3 level without the presence of hypotension, rhabdomyolysis, hemolysis, or use of nephrotoxic agents, making acute glomerulonephritis very likely, albeit in the absence of confirmatory histopathology (Ghosh *et al,* 2011; Bhagat *et al,* 2012).

These interesting cases highlight the possible immunopathogenic mechanism of glomerular and tubular damage either by immune complex-mediated mechanism or cytokine-mediated tubular injury.

Autoimmunity induced by molecular mimicry is another possible mechanism for dengue-associated renal disease since this phenomenon has also been reported in other viral infections, namely coxsackie virus and Epstein-Barr virus (Lin *et al,* 2011). Autoantibodies against platelets, endothelial cells, and coagulatory molecules have been demonstrated in patients with dengue virus infection and are believed to result from cross-reactivity to dengue virus antigen; that is, NS1, prM, and E proteins, respectively. These antibodies can cause platelet dysfunction, endothelial injury, and coagulopathy upon binding to their corresponding antigens. An example of autoimmunity and AKI came from a report of an elderly woman presenting with DHF and AKI in Honduras with serologically and pathologically confirmed anti-glomerular basement membrane (GBM) disease in association with positive P-ANCA, and anti-myeloperoxidase antibody on serologic studies (Lizarraga *et al,* 2015). Development of auto-antibodies to GBM or neutrophil antigen is believed to be induced by environmental factors including infection (Tarzi *et al,* 2011), which was possibly dengue virus infection in this Honduran patient.

Hemolytic-uremic syndrome

Hemolytic-uremic syndrome is another rare manifestation of dengue infection. There have been three reported cases (Wiersinga *et al,* 2006; Hadianto and Mellyama, 2011; Aroor *et al,* 2014). Patients presented with a triad of thrombocytopenia, hemolytic anemia, and AKI. One patient had renal biopsy, and it found microthrombi in the glomeruli. Electron microscopy showed microtubuloreticular structure, suggesting viral infection (Wiersinga *et al,* 2006).

Abnormal urinalysis

There is an abnormal urinalysis in up to 90%, increasing with dengue severity, mostly self-limiting subnephrotic range proteinuria in up to 71% and microscopic hematuria in up to 80% (Futrakul *et al,* 1973; Kuo *et al,* 2008; Lumpaopong *et al,* 2010; Vachvanichsanong *et al,* 2010).

There are four cases of reported nephrotic-range proteinuria without nephrotic syndrome that disappeared on resolution of dengue virus infection suggesting association of proteinuria with the disease process (Vasanwala *et al,* 2009; Hutsopardol *et al,* 2011; Hebbal *et al,* 2016). Moreover, patients who developed significant proteinuria defined by spot urine protein creatinine ratio of 0.2 g/g or more had association with higher degree of thrombocytopenia compared to those without significant proteinuria and higher peak proteinuria (0.56 *vs* 0.08 g/day; $p<0.001$) was associated with the development of DHF/DSS. As

a result, monitoring of urine protein to identify peak proteinuria has been proposed to predict development of DHF/DSS (Vasanwala *et al,* 2011).

Microscopic hematuria must be differentiated between glomerular and non-glomerular hematuria due to bleeding disorder or catheterization. Glucosuria, ketonuria, and abnormal tubular casts were also found, suggesting tubular injury after dengue viral infection (Futrakul *et al,* 1973).

Glomerulopathy

Multiple evidences from animal and human studies supported the causal relationship between dengue virus infection and various types of glomerulopathy. Barreto *et al* (2004) demonstrated in mice infected by dengue virus type 2 that 48 hours after the onset of infection, there were glomerular enlargement, endocapillary and mesangial hypercellularity together with glomerular IgM deposition. Similarly, Boonpucknavig *et al* (1981) studied renal histopathology in dengue virus type 2-infected mice at the end of the third week of infection and observed immune-complex deposition as well as proliferative lesions in the glomeruli.

Another study demonstrated IgG, IgM, and C_3 deposition in 50% of patients with dengue virus infection and renal abnormalities (Boonpucknavig *et al,* 1976). Ultrastructural examination under transmission electron microscope revealed glomerular immune-complex-type deposits associated with mesangial cell hypertrophy and the presence of dense spherical particles ranging from 40-50 nm in diameter, possibly dengue virus particles, in 60% of patients.

Other pathological patterns have also been reported. IgA-dominant immune complex deposition with mesangial proliferation presenting with hematuria and proteinuria was documented with resolution of mesangial proliferation and IgA deposition six weeks later (Upadhaya *et al,* 2010). One patient presented with rapidly progressive glomerulonephritis with serum positive for anti-myeloperoxidase and anti-glomerular basement membrane (GBM) antibodies. Renal biopsy revealed diffuse crescentic glomerulonephritis. Immunofluorescence examination demonstrated strong linear IgG deposition along capillary walls. A diagnosis of anti-GBM with anti-neurtophilic cytoplasmic antibody (ANCA) was made (Lizarraga *et al,* 2015). The proliferative pattern with hypocomplementemia has also been reported (Bhagat *et al,* 2012). Another young female presented with nephritonephrotic features with hypocomplementemia. Renal biopsy showed diffuse proliferative glomerulonephritis consistent with lupus nephritis (Rajadhyaksha and Mehra, 2012). Table 2 summarizes the pathological patterns of dengue virus infection in each structure of the kidney.

Electrolyte abnormalities

Electrolyte disturbances are common in dengue infection, yet might be frequently unreported. Higher electrolyte imbalances were associated with dengue severity: 25.1 % with DF, 33.5 % with DHF, and 39.8 % with DSS (Vachvanichsanong *et al,* 2015). The most common electrolyte disturbances are hyponatremia and hypokalemia (Futrakul *et al,* 1973; Kuo *et al,* 2008; Lumpaopong *et al,* 2010; Bunnag and Kalayanarooj, 2011). Hyponatremia may be from plasma leakage, hypotonic therapy, or renal loss. Hyponatremia was reported in 66% of 150 children. Fifty percent of the cases had mild hyponatremia (serum Na 130-134 mEq/l), 14.7% had moderate hyponatremia (serum Na 125-129 mEq/l), and 1.3% had profound hyponatremia (serum Na <125 mEq/l) (Lumpaopong *et al,* 2010). Hyperkalemia is possibly due to rhabdomyolysis or AKI. Interestingly, a case series by Bunnag and Kalayanarooj (2001) reported a high prevalence of hypocalcemia in patients with DSS. Metabolic acidosis is another frequent complication found in 8.6-14% possibly due to hypoperfusion or hyperchloremia after saline infusion (Lumpaopong *et al,* 2010; Vachvanichsanong *et al,* 2015).

Management

In the vast majority of cases, dengue-associated renal disorders are self-limiting. Intensive monitoring for early diagnosis of complications and supportive care according to dengue staging is the mainstay of patient care. Blood urea nitrogen, creatinine, and creatinine-kinase phosphate

Table 2. Renal pathology in dengue infection.

Tubules
• Red blood cells in tubular lumens • Acute tubular necrosis
Glomeruli
• Immune complex of IgG, IgM and C_3 deposited in the glomeruli also with focal thickening of the glomerular basement membrane and mesangial hypertrophy • Glomerular enlargement as well as increased endocapillary and mesangial cellularity • Proliferative lesions • IgA, lupus nephritis, and anti-GBM (rare)
Interstitium
• Acute interstitial nephritis
Vessels
• Thrombotic microangiopathy

monitoring is advisable. Frequent volume status assessment and judicious fluid administration is mandatory. Based on the three randomized controlled trials in children, colloid has no clear advantage over crystalloid regarding the overall outcomes. Therefore, crystalloid is still the fluid of choice in severe dengue infection. Colloid, however, may restore blood pressure rapidly in patients with refractory shock with a pulse pressure less than 10 mmHg (Dung *et al,* 1999; Ngo *et al,* 2001; Wills *et al,* 2005). The amount of fluid should be minimized to maintain hemodynamic stability but prevent plasma leakage. Corticosteroid is not recommended for severe dengue (Zhang and Kramer, 2014). Renal replacement therapy (RRT) should be started in patients with persistent volume overload, refractory/severe hyperkalemia, refractory acidosis, or uremia despite a maximally conservative strategy. There are no data regarding time-to-initiate, dosing, or modes of RRT in severe AKI, which suggests further studies as to whether continuous RRT for gradual volume removal can improve clinical outcomes are needed. Hemodialysis maybe preferred to peritoneal dialysis due to bleeding disorder accounted by dengue virus infection, which may prohibit Tenchkoff catheter insertion.

CONCLUSION

AKI following dengue viral infection is one of the most significant complications of dengue. The incidence of AKI increases with more severe dengue. Apart from ATN, rhabdomyolysis and hemolytic-uremic syndrome are rare but deadly adverse events. Non-specific proteinuria and hematuria can occur in dengue infection although some patients experience acute glomerulonephritis. Electrolytes must be monitored because dysnatremia, dyskalemia, and acid-base disturbances are common. RRT should be initiated as per conventional indications. Finally, further studies should focus on clarifying the pathogenesis of AKI in dengue and using novel biomarkers to assist in improving clinical outcomes.

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