

# Renal Injury in Dengue Viral Infections

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## ABSTRACT

Dengue virus infection (DVI), a tropical disease, caused by the bite of female *Aedes aegypti* and *Aedes albopictus* mosquitoes. The four distinct virus serotypes of the Flaviviridae family, DENV-1, DENV-2, DENV-3 and DENV-4, cause DVI. Dengue virus infection presents in different ways, ranging from a relatively innocuous flu-like dengue fever to severe dengue. Severe dengue fever is often associated with renal injury ranging from a mild and transient elevation of serum creatinine (SCr), proteinuria, erythrocyturia, dyselectrolytemia, glomerulonephritis, nephrotic syndrome to acute kidney injury (AKI). Acute kidney injury, an infrequent complication of dengue, is usually associated with hypotension, rhabdomyolysis, or hemolysis. Sadly, the existence of renal injury in DVI and its role in the outcome is rarely recognized in clinical practice. This review is to remind ourselves to this overlooked entity of renal manifestations of dengue infection in the tropics.

**Keywords:** Acute kidney disease, Acute kidney injury, Chronic kidney disease, Dengue viral infections, Mortality, Renal replacement therapy, Restricted fluid resuscitation.

*Pediatric Infectious Disease* (2020): 10.5005/jp-journals-10081-1227

## RENAL INJURY IN DENGUE FEVER

Dengue viral infection (DVI) is a viral disease that is transmitted by mosquitoes and has rapidly spread in all tropical regions. The female mosquitoes mainly of the species *Aedes aegypti* and, to a less extent, *Aedes albopictus* transmit the dengue virus. These mosquitoes are also vectors of chikungunya, yellow fever, and Zika viruses. DENV-1, DENV-2, DENV-3, and DENV-4 are the four distinct serotypes of dengue virus of the Flaviviridae family causing dengue. The individual gets lifelong immunity against that particular serotype on recovery from the infection. However, there is only partial and temporary cross-immunity to the other serotypes after recovery. WHO Fact sheet; Nov 2019.<sup>1</sup> The adaptive immune response to natural DVI increases the risk of developing severe dengue with subsequent infections (secondary infection by other serotypes).<sup>2</sup>

Dengue viral infection is classified according to the World Health Organization guidelines (2009) as dengue with or without warning signs and severe dengue with severe morbidity and mortality. Severe dengue is defined as dengue with any of the following: (1) severe plasma leakage leading to shock, the dengue shock syndrome (DSS) or respiratory distress; (2) severe systemic bleeding, the dengue hemorrhagic fever (DHF); and (3) any organ failure, e.g., elevated liver enzyme levels, impaired consciousness, or heart failure.<sup>3</sup> Strangely, renal involvement is least appreciated area of DVI though it contributes significantly to its severity.

### Tentacles of DVI

Multiple organ dysfunction involving liver, muscles, heart, brain, and kidneys is seen in DVI. A variety of renal manifestations such as proteinuria, hematuria, glomerulonephritis, and acute kidney injury (AKI) are reported during or shortly after acute DVI. The incidence of the above renal manifestations varies between 17 and 62% in patients with DVI.<sup>4</sup>

A general feature of kidney involvement is an abnormal urinalysis. A very early study, in 1973, of 24 children presented with abnormal urinalysis in DVI. Proteinuria, glycosuria, ketonuria, occult blood, microscopic hematuria, and an abnormally high number of

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**How to cite this article:** Sudha E, Sangeetha G, Nammalwar BR. Renal Injury in Dengue Viral Infections. *Pediatr Inf Dis* 2020;2(1):6–11.

**Source of support:** Nil

**Conflict of interest:** None

tubular cells were found in 71, 19, 38, 38, 80, and 90% of the cases, respectively.<sup>5</sup>

### Proteinuria

Increased urinary excretion of protein and plasma leakage in complicated forms of DVI is due to disruption of glycocalyx (see later) that coats the glomerular and vascular endothelial cells and is due to direct action of the virus or by the NS1 antigen.<sup>6,7</sup> Self limited proteinuria that disappears together with the resolution of the disease has been reported in up to 74% of patients with DHF.<sup>3</sup> In a study of 2,416 adult patients, with DVI the incidence of renal manifestations (proteinuria, hematuria, and AKI) was as high as 9.59%. Proteinuria was defined as urinary protein >1+ (30 mg/dL) by dipstick test. A total of 218 (9.56%) patients were found to have proteinuria. Nephrotic-range proteinuria was seen in 5 patients (2.16%).<sup>8</sup> The analysis of urine protein creatinine ratio (UPCR) at admission in 52 children with DVI, proteinuria was detected in 23.1% (n = 12) of the cases. Notably none of the children without DVI warning signs had proteinuria compared with 16.1% (5/31) with warning signs and 50% (7/14) in patients with severe dengue. The highest level of UPCR occurred at the end of the critical phase of the disease and tends to decrease with the beginning of the recovery

phase. UPCR measurement seems to be useful for monitoring the progress of disease than as a triage at the first time examination.<sup>9</sup>

### Hematuria

Hematuria was seen in about 30% of patients with DVI.<sup>10,11</sup> It is unclear from the available studies whether the hematuria in DVI is glomerular or non-glomerular but is presumed to be glomerular. The significance of its presence in DVI is unknown at present. But it is to be remembered that glomerular hematuria is a marker of the glomerular filtration barrier dysfunction or damage.<sup>12</sup> In a study of 18 adult patients with DVI, 5 (27.78%) had microscopic hematuria; 2 of these 5 patients had 2+ hematuria [6–10 (RBCs/HPF)]. Four patients had both proteinuria and hematuria.<sup>10</sup> The records of 100 hospitalized DVI cases were retrospectively examined. Urinalysis results were recorded for 87 of the patients; hematuria was detected in 31% and protein in 74%.<sup>11</sup> In a cohort study of 154 adults and 147 children with DVI, the prevalence of a positive urine blood test was similar between the children and adults (55 vs 58%), although some clinical symptoms were different. However, it is unclear in this study whether the positive urine blood test was due to hemoglobinuria, myoglobinuria, or hematuria.<sup>13</sup>

### Abnormal Urinalysis

The prevalence of abnormal findings in urinalysis in DVI in two studies from Thailand as summarized by Prayong Vachvanichsanong P and McNeil E is given in Table 1. Note urinary abnormalities (UA) are increased in severe DVI.

### Glomerulonephritis

In humans and mouse models, there have been reports of various types of glomerulonephritis during or shortly after dengue infection. One case study reports transient IgA nephropathy in a 15-year-old boy admitted with DVI complicated by dialysis-dependent AKI. Microscopic glomerular hematuria and proteinuria were revealed on examination of urine. Mesangial proliferation with mesangial IgA-dominant immune complex deposits and acute tubular necrosis (ATN) were seen in the kidney biopsy. Reversal of glomerular changes with resolution of mesangial IgA deposits were evident at 6 weeks after clinical recovery on a repeat kidney biopsy.<sup>16</sup> It is possible that these authors were actually reporting a case of IgA-dominant postinfection glomerulonephritis (PIGN). IgA-dominant PIGN presents with AKI, hematuria, and proteinuria and typically manifests after infection. Variable light microscopic findings are seen on renal biopsy which range from diffuse proliferative glomerulonephritis to mesangial hypercellularity, dominant or codominant IgA deposits by immunofluorescence, and frequently, but not always, subepithelial “hump”-shaped electron-dense deposits. Currently, organisms other than methicillin-resistant *Staphylococcus* have

also been noted. Hence, it is termed as “infection-related” IgA-dominant PIGN.<sup>17</sup>

In a report of 20 adult patients with DHF and renal derangement, a renal biopsy was done in the second week after the onset of fever. In 10 cases, IgG or IgM, or both, and C3 could be localized in the glomeruli. The electron microscopy showed thickening of the glomerular basement membrane, with hypertrophy of mesangial cells at the sites where the immune complex were identified. Dense, spherical particles, 40–50 nm in diameter, were found in 12 cases.<sup>18</sup> These findings strongly indicate an immune-mediated process of renal injury in DVI. In all these cases, the symptoms resolved with return of normal urinary findings.

In a recent autopsy study of renal tissue, multiple histopathological changes have been identified confirming renal injury in DVI. There were diffuse mononuclear infiltration around the glomerulus in the cortical region and also in the medullary vessels, arteriolar hyalinosis, lymphocytic infiltrate, increased capsular fibrosis, proximal convoluted tubule damage, edema, debris formation, and thickening of the capillary basement membrane. It is postulated that a high systemic viral load along with exacerbated host immune response is the cause for renal tissue injury.<sup>19</sup>

### Electrolytes and Acid–base

The regulation of fluid, electrolyte, and acid–base balance is primarily done by the kidneys. Dyselectrolytemia, hypermagnesemia, hyperphosphatemia, hypocalcemia, bicarbonate deficiency (metabolic acidosis), raised serum creatinine (SCr), and blood urea nitrogen (BUN) tend to develop in those patients with AKI. On fluid retention, the sodium is generally retained, but dilution makes it appear normal or hyponatremic.

In a study of 202 adults, on the day of admission, 81 patients (40.09%) had serum sodium levels within normal limits, 110 (54.45%) had mild hyponatremia, 5 (2.47%) patients had moderate hyponatremia, and 6 (2.97%) patients reported to have severe hyponatremia. Potassium levels remained within normal range in majority of patients (112, 55.44%). In total, 67 patients (33.16%), 12 patients (5.94%), 6 patients (2.9%), and 5 patients (2.47%) reported mild, moderate, severe hypokalemia, and hyperkalemia, respectively. Mild hyponatremia and hypokalemia was noted in children with dengue fever. In children with DSS and DHF, a higher frequency of moderate to severe hyponatremia and hypokalemia was observed.<sup>20</sup>

The term “acute renal failure” (ARF) is replaced by AKI. Acute renal injury is defined by an increase in SCr > 0.3 µg/dL within 48 hours or ≥1.5 times baseline or urine output (UO) < 0.5 mL/kg/hour for 6 hours.<sup>21</sup> This definition ensures staging of the severity of renal injury as stages I, II, or III (Table 2). This in turn ensures early interventions to arrest its progress, institute fluid replacement, avoid nephrotoxic medications, and determine renal replacement therapy (RRT).

In recent years, AKI is no longer considered as an isolated event but often as a primary cause of remote organ dysfunction in the lungs, heart, liver, intestines, and brain through a proinflammatory mechanism that involves neutrophil cell migration, cytokine expression, and increased oxidative stress. It would be appropriate to redefine AKI from single organ failure syndrome, to a syndrome where the kidney plays an active role in the evolution of multiorgan dysfunction syndrome (MODS).<sup>22</sup>

### ACUTE KIDNEY INJURY IN DVI (dAKI)

A prospective study of 198 children with DVI showed that a SCr level > 4.6 µg/dL was associated with severe dengue.<sup>23</sup> In another

**Table 1:** Prevalence of abnormal findings in urinalysis in dengue virus infection<sup>14,15</sup>

	Lumpaopong et al., 2010		Vachvanichsanong et al., 2010
	Dengue fever (n = 67) (%)	DHF (n = 73) (%)	DF + DHF + DSS (n = 1,342) (%)
Abnormal UA	–	–	28.50
Glycosuria	–	–	3.70
Hematuria	18	27	6.30
Proteinuria	15	27	22.10

**Table 2:** Acute kidney injury is staged for severity according to the following criteria<sup>21</sup>

Stage I	1.5–1.9 times baseline or $\geq 0.3$ $\mu\text{g/dL}$ absolute increase in SCr	Urine volume $< 0.5$ mL/kg/hour for 6–12 hours
Stage II	SCr $\geq 2.0$ –2.9 times baseline	Urine volume $< 0.5$ mL/kg/hour for $\geq 12$ hours
Stage III	SCr $\geq 3.0$ times from baseline or increase in SCr to $\geq 4.0$ $\mu\text{g/dL}$ OR initiation of RRT OR in patients $< 18$ years, decrease in eGFR to $< 35$ mL/minute/1.73 m <sup>2</sup>	Urine volume $< 0.3$ mL/kg/hour for $\geq 24$ hours or anuria for $\geq 12$ hours

SCr, serum creatinine; eGFR, estimated glomerular filtration rate

study of 617 children under 13 years of age classified as having DHF: 48% were males, 0.3% newborns, 11.8% infants, 23% preschool children, and 64.9% schoolchildren. Uncommon manifestations were hepatitis, encephalopathy, acalculus cholecystitis, ARF, hemophagocytic syndrome, and coinfections.<sup>24</sup> In a retrospective study of 2,893 Thai children under 15 years during 1989–2007, DHF-caused AKI was estimated to be 0.9% (25/2,893) of admissions, with a high mortality rate of 64.0%, whose mean SCr was  $> 4.9$   $\mu\text{g/dL}$ . In 24 of the above 25 patients with AKI were identified to have both DSS and DHF. Of the 25 patients with DHF-associated AKI, 16 (64%) died as a result of profound shock, together with other conditions such as liver failure, respiratory failure, and severe bleeding supporting the view that AKI could be the causative factor in this MODS.<sup>25</sup>

An unpublished data of dengue dAKI from the Department of Pediatric Medicine, Sri Ramachandra Institute of Higher Education and Research, Chennai, have shown that during the period January 2019 and December 2019, of 319 children with DVI, 127 children needed intensive care. Among the 127 patients, 26 (20.5%) children developed AKI. The age-wise distribution of dAKI children was  $< 1$  year ( $n = 4$ ; 25%), 1–5 years ( $n = 8$ ; 28.6%), 6–10 years ( $n = 5$ ; 13.2%), and more than 10 years ( $n = 9$ ; 20%), demonstrating an increasing tendency for both DVI and dAKI with age. Children with severe DVI developed a higher number of AKI ( $n = 20$ ; 28.6%), when compared with children with DVI with warning signs along ( $n = 6$ ; 11.8%) with the significant  $p$  value of 0.03. All the six children with DVI alone had normal renal function. More number of children was seen in stage I with progressive less number in stages II and III. Twenty-six children had microscopic hematuria, 23 had proteinuria, and 4 children had glycosuria indicating glomerular damage and possibly associated renal tubular injury. Importantly in agreement with publications, the risk factors for the development of dAKI included the need for colloids infusion, inotropic support, ventilatory requirement, and presence of secondary hemophagocytic lymphohistiocytosis (HLH) (Table 3). Nine children with AKI underwent dialysis [peritoneal dialysis (PD): five, hemodialysis: three, and continuous renal replacement therapy (CRRT): one]. Among 26 children with AKI, 23 recovered and 3 died (mortality was 11.5%). Mortality in non-AKI group was 1 (1%). Two children who underwent PD and one child on CRRT did not survive. All these three children had MODS.

### Incidence of AKI

The reported incidence of AKI in various studies varied from 0.9 to 14.2%.<sup>25–27</sup> The difference in the incidence may be due to the difference in staging criteria used by these studies. Two studies showed the highest incidence of 14.2 and 13.3%, respectively. Both

**Table 3:** Presenting predisposing factors for dAKI

	AKI (%)	No AKI (%)	$p$ value
Ventilated	9 (47.4)	10 (52.6)	0.002
Not ventilated	17 (15.7)	91 (84.3)	
Inotropic support	8 (72.7)	3 (27.3)	0.000
No inotropes	18 (15.5)	98 (84.5)	
HLH	11 (36.7)	19 (63.3)	0.012
No HLH	15 (15.5)	82 (84.5)	

the studies used AKIN staging for defining AKI.<sup>27,28</sup> In the data from Sri Ramachandra Institute of Higher Education and Research, the incidence was higher as it had included only children admitted in ICU.

In a pediatric population during a 19-year period, 2,893 patients  $< 15$  years of age needed hospitalization due to clinically diagnosed DVI. Among these children, AKI was seen in 25 (0.9%) patients, and 16 of 25 (64.0%) of these patients died. Male children constituted 56% (14 of 25), and the median age of all was 10 years (range, 6 months to 13.1 years).<sup>25</sup> The incidence of complicated renal dysfunction was found to be 0.3% in a mixed population which included 6,154 DHF patients whose ages were not mentioned.<sup>29</sup> Another study showed 3.3% of ARF in 304 adults with DHF.<sup>30</sup> Acute kidney injury was present in 13.3% (71/532) of adult patients. Mild AKI and moderate-to-severe AKI was seen in 64.8 and 35.2% of these patients, respectively.<sup>28</sup>

### Mechanism of Renal Injury in DVI<sup>26,31</sup>

In the community-acquired AKI, the cause is commonly monogenic. The mechanisms of AKI and renal injuries in DVI are polygenic. Infections cause renal damage through:

- Cytopathic injury caused by direct invasion of the offending microorganisms.
- Circulating or *in situ* immune complexes caused by the immune mechanisms against the microbial antigens as in viral glomerulonephritis.
- Perturbations in innate and cellular immunity as in infection-related glomerulonephritis.
- Multi-organ failure caused by sepsis.
- Hemolysis, rhabdomyolysis, and as hepatorenal syndrome.
- Rarely from ATN as a consequence of hypovolemia and capillary leak causing ATN and thus rarely cause AKI.
- Therapeutic use of nephrotoxic antimicrobials.

### Risk Factors for dAKI

The various risk factors independently associated with AKI development were male gender (OR: 2.7), DHF (OR: 8), rhabdomyolysis (OR: 7.9), multiple organ dysfunction (OR: 17.9), diabetes mellitus in adults (OR: 10.5), delayed hospital consultation (OR: 2.1), and use of nephrotoxic drugs (OR: 2.9). It also includes elevated liver enzymes, low serum albumin, decreased serum bicarbonate, coexisting bacterial or viral infection, preexisting renal parenchymal injury, hemoconcentration, sepsis, obesity, severe DVI, and older age.<sup>27</sup>

### AKI and mortality in DVI

In a prospective study from January 2002 through January 2003, 519 dengue-infected patients were enrolled, of which 412 patients had classical DVI and 107 patients had DHF/DSS. Twenty-one (4.0%)

patients were in the renal failure (RF) group, and it was statistically proven that higher mortality was seen in RF group. In this outbreak, 12 patients had died, and all of them had DHF/DSS. The severity of GFR impairment was associated with higher percentages of DHF/DSS ( $p = 0.029$ ) and mortality. This study concludes that in DHF/DSS, patients with RF had complicated clinical courses with a higher mortality rate.<sup>32</sup>

In yet another study, dAKI was seen in 82 patients (3.4%), of whom 58 (70.73%) had AKIN-I, 19 (23.17%) had AKIN-II, and 5 patients (6.09%) had AKIN-III. Death occurred in 11 patients (39.28%) with dAKI, and those with dAKI had significant morbidity, mortality, longer hospital stay, and poor renal outcomes.<sup>8</sup>

## Management of dAKI

### Prevention

Acute kidney injury in DVI is uncommon as an isolated phenomena.<sup>33</sup> Dedicated monitoring of urine output is a useful clinical method to identify the onset of AKI. "Triage, monitoring and prognostication based on early detection of decrease in UO is fundamental not only for avoiding and preventing AKI, but also for tracking volume overload and assessing response to therapy".<sup>34</sup> This does not deny the need for serial SCr monitoring in high-risk patients. Acute kidney injury is often preceded by DSS or DHF. Hence, the primary preventive care involves appropriate fluid management and proactive treatment of hemorrhage for maintaining effective arterial blood volume (EABV). Presently, EABV deficit is corrected with isotonic crystalloid (normal saline) boluses of 10 mL/kg over 20 minutes and is repeated until improvement in EABV. The fluid therapy in DSS has to be done cautiously with serial monitoring as there is a risk of fluid overload (FO). The FEAST trial has demonstrated that resuscitation therapy with normal saline exceeding 60 mL/kg results in edema, hyperchloremic acidosis, reduced hemoglobin concentration, increased requirement for higher ventilation pressures, and worsening of neurological function.<sup>35</sup> These warnings can also be considered in the fluid therapy of DSS.

In a recent study in patients aged between 2 months and 16 years who remained in shock despite 30 mL/kg crystalloid over 3 hours (crystalloid refractory shock crystalloid not qualified), colloid was used for volume replacement, provided hemorrhage had been ruled out. Albumin was the preferred colloid in addition to crystalloids. The limitation of resuscitation fluid has been found to decrease positive FO, occurrence of abdominal compartment syndrome, lower intubation and positive pressure ventilation requirements, major hemorrhage, and AKI, which in turn reduced pediatric intensive care unit (ICU) stays and mortality.<sup>36</sup> For a more comprehensive information on fluid management in DVI, see Gan and National Guidelines for Clinical Management of Dengue Fever.<sup>37,38</sup>

Fluid overload can damage the endothelial glycocalyx layer (EGL) and consequent worsening of intravascular fluid extravasations and interstitial edema and MODS including kidneys. EGL is a web of membrane-bound glycoproteins and proteoglycans which binds to plasma proteins on the luminal surface of endothelium and effectively excludes proteins from the subendothelial space, thereby resulting in a local oncotic gradient between plasma and subendothelial space, which opposes transcapillary efflux into the interstitium.<sup>39</sup> Additionally, studies recommend serial monitoring of SCr phosphokinase for early diagnosis of rhabdomyolysis and plan preventive measures.<sup>40,41</sup>

### Management

Once a diagnosis of AKI is established, the physician is caught between the horns of dilemma. Paradoxically, DSS and DHF need volume administration to maintain EABV, while dAKI needs fluid restriction to avoid FO. It is wise to prioritize maintaining the EABV and seek early RRT.<sup>42</sup> In the presence of stable hemodynamic status in children with oliguria and not anuria, some authors prefer to give a trial of furosemide infusion.<sup>43</sup>

### Timing of RRT

There is no consensus guidelines for optimal timing to initiate RRT or biochemical cutoff values for initiation of RRT in dAKI. Literature suggests that CRRT should be initiated at a FO of >20% as 10–20% FO represents a critical threshold at which outcomes are adversely impacted.<sup>44</sup> Most often, the indications are FO exceeding 10% of hospital admission body weight unresponsive to diuretic therapy, followed by hyperkalemia, refractory hyponatremia, metabolic acidosis, and persistent anuria.

### Type of RRT

Options for RRT therapy for AKI include PD and various forms of extra corporeal dialysis procedures: intermittent hemodialysis (IHD), CRRT, and newer "hybrid" therapies known as prolonged intermittent RRT or sustained low-efficiency dialysis. Presently, the procedures are PD in small children, IHD in older and bigger children, and CRRT limited to a few centers with dedicated dialysis units. To the best of our knowledge, there are no comparative studies, in dAKI, to assess the benefit one over the other in the extra corporeal dialysis procedures. CRRT should be a preferred modality in dAKI as these are hemodynamically unstable patients with FO and paradoxically need further intravenous fluid therapy. The advantage of CRRT includes gradual continuous volume removal, control of volume status easier, and allows administration of medications and nutrition with less concern for FO. Because it is a continuous modality, there is a better control of SCr, electrolytes, and acid–base status as there is less fluctuation of solute concentrations over time. The main disadvantages of CRRT include extended nurse time, cost, vascular access, filter clotting, and the consequent need for anticoagulation.

### Outcome in dAKI

The outcome as assessed by immediate hospital mortality, residual renal injury (persistent erythrocyturia, proteinuria, and low eGFR) termed as acute kidney disease (AKD), and progression to chronic kidney disease (CKD) are not available with strong data, particularly in children.

### Immediate mortality in dAKI needing RRT

A total of 1,484 patients were included in a study, with 71 (4.8%) categorized into the AKI group. A total of 10 (14.1%) patients with AKI received hemodialysis, among which 9 (12.7%) patients from the AKI group died.<sup>45</sup> In another study of 3,525 DVI adult patients, 43 (1.21%) developed AKI. Hemodialysis was required on arrival in 31 (72.09%) patients. Complete recovery seen in 37 (86%), while 6 (14%) died during acute phase of illness.<sup>46</sup> Heterogeneous clinical picture and modalities of treatment make it difficult to establish a definitive mortality incidence in dAKI.

### AKD

Persistence of evidence of renal injury post-AKI is grouped as AKD. In a recent study in adults with dAKI in India, among 620 adults,

90 (16.3%) patients developed AKI. In total, 14 patients out of 20 patients with AKI requiring dialysis died after two to three dialysis sessions. In a majority of these, 11 patients out of 14 patients died of shock caused by intractable bleeding or severe DHF/DSS-induced MODS and 3 patients died of secondary infection. None of the deaths were due to complications of AKI. A complete recovery of kidney function was seen among 75 patients (83.33%) of AKI, and some degree of renal dysfunction was persisting among 15 (16.66%) patients of AKI at the time of discharge.<sup>47</sup> Renal recovery was assessed by using recovery criteria based on levels of SCr and eGFR during the post-discharge period for 3 months among these AKI patients. Surprisingly, about 50% patients ( $n = 36/71$ ) with AKI had eGFR that could be grouped as CKD stage II, while 18.3% ( $n = 13/71$ ) and 4.2% ( $n = 3/71$ ) patients had eGFR corresponding to advanced stages III and IV of CKD.<sup>48</sup>

### Chronic Kidney Disease

Dengue adult patients who particularly developed dialysis-dependent AKI and recovered have demonstrated delayed long-term incidence of CKD.<sup>49</sup> To know whether this is true in pediatric practice, as children are expected to have a larger renal reserve, readers are recommended to refer reference no. 50.<sup>50</sup> Acute kidney injury from DVI could be a potential risk factor for CKD in children. These children need annual monitoring of weight, blood pressure, urine for albuminuria and if needed a BUN and SCr until adolescence.

### CONCLUSION

The presence of renal injury, proteinuria, hematuria, and dyselectrolytemia, including features of glomerulonephritis, are poorly recognized entities in children with DVI. Studies have documented histopathological evidence renal injury. All renal manifestations are not associated with increased mortality, though they may be associated with increased severity of DVI. AKI in DVI is associated with increased mortality independent of the associated DHF and DSS.<sup>51</sup> Prompt intervention and initiation of RRT on time can change the clinical outcome, immediate mortality, and long-term morbidity. These children need long-term follow-up for possible later CKD.

### ACKNOWLEDGMENTS

Authors thank Professor and Head Dr S Shuba, and Professor Dr P Ramachandran, Department of Pediatric Medicine, Sri Ramachandra Institute of Higher Education and Research, for providing their data.

### REFERENCES

1. Fact sheets. Dengue and severe dengue - World Health Organization. Nov 4, 2019.
2. Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. *Rev Immunol* 2011;11(8):532–543. DOI: 10.1038/nri3014.
3. Srikiatkachorn A, Rothman AL, Gibbons RV, et al. Dengue—how best to classify it. *Clin Infect Dis* 2011;53(6):563–567. DOI: 10.1093/cid/cir451.
4. Lizarraga KJ, Nayer A. Dengue-associated kidney disease. *J Nephropathol* 2014;3(2):57–62. DOI: 10.12860/jnp.2014.13.
5. Futrakul P, Poshyachinda V, Mitrakul C, et al. Renal involvement and reticulo-endothelial-system clearance in dengue hemorrhagic fever. *J Med Assoc Thai* 1973;56(1):33–39. (Cross reference).
6. Wills BA, Oragui EE, Minh Dung N, et al. Size and charge characteristics of the protein leak in dengue shock syndrome. *J Infect Dis* 2004;190(4):810–818. DOI: 10.1086/422754.
7. Simmons CP, Farrar JJ, Chau Nguyen VV, et al. *N Engl J Med* 2012;366(15):1423–1432. DOI: 10.1056/NEJMra1110265.
8. Eswarappa M, Reddy SB, John MM, et al. Renal manifestations of dengue viral infection. *Saudi J Kidney Dis Transpl* 2019;30(2):394–400. DOI: 10.4103/1319-2442.256847.
9. Andries AC, Duong V, Cappelle J, et al. Proteinuria during dengue fever in children. *Int J Infect Dis* 2017;55:38–44. DOI: 10.1016/j.ijid.2016.12.022.
10. Singh D, Kapoor AK, Yadav P, et al. Dengue fever patients may develop proteinuria and hematuria – A report of 18 patients. *J Med Sci Clin Res* 2017;5(7):25785–25790. DOI: 10.18535/jmscr/v5i7.242.
11. Horvath R, McBride WJH, Hanna J. Clinical features of hospitalized patients during dengue-3 epidemic in far north Queensland 1997–1999. *Dengue Bulletin* 1999;23:24–29.
12. Moreno JA, Martin-Cleary C, Gutierrez E, et al. Haematuria: the forgotten CKD factor? *Nephrol Dial Transplant* 2012;27(1):28–34. DOI: 10.1093/ndt/gfr749.
13. Hanafusa S, Chanyasanha C, Sujirarat D, et al. Clinical features and differences between child and adult dengue infections in Rayong Province, Southeast Thailand. *Southeast Asian J Trop Med Public Health* 2008;39(2):252–259.
14. Vachvanichsanong P, McNeil E. Electrolyte disturbance and kidney dysfunction in dengue viral infection. *Southeast Asian J Trop Med Public Health* 2015;46(Suppl. 1):108–117.
15. Lumpaopong A, Kaewplang P, Watanaveeradej V, et al. Electrolyte disturbances and abnormal urine analysis in children with dengue infection. *Southeast Asian J Trop Med Public Health* 2010;41(1):72–76.
16. Upadhaya BK, Sharma A, Khaira A, et al. Transient IgA nephropathy with acute kidney injury in a patient with dengue fever. *Saudi J Kidney Dis Transpl* 2010;21(3):521–525.
17. Gaut JP, Muelle S, Liapis H. IgA dominant post-infectious glomerulonephritis update: pathology spectrum and disease mechanisms. *Diagn Histopathol* 2017;23(3):126–132. DOI: 10.1016/j.mpdhp.2017.03.010.
18. Boonpucknavig V, Bhamarapavati N, Boonpucknavig S, et al. Glomerular changes in dengue hemorrhagic fever. *Arch Pathol Lab Med* 1976;100(4):206–212.
19. Nunes PCG, Rioja LS, Coelho JMCO, et al. Renal injury in DENV-4 fatal cases: viremia, immune response and cytokine profile. *Pathogens* 2019;223(8):2–11. DOI: 10.3390/pathogens8040223.
20. Vinay KG, Virendra PC, Ami B, et al. Study of electrolyte disturbances in dengue infected patients. *Int J Contemp Med Res* 2019;6:B5–B8.
21. Kellum JA, Lameire N, Aspelin P. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;2(1):1–138. DOI: 10.1038/kisup.2012.1.
22. Shiao CC, Wu PC, Huang TM, et al. National Taiwan university hospital study group on acute renal failure and the Taiwan consortium for acute renal diseases. long-term remote organ consequences following AKI. *Crit Care* 2015;19(438):1–11.
23. Phakhounthong K, Chaovalit P, Jittamala P, et al. Predicting the severity of dengue fever in children on admission based on clinical features and laboratory indicators: application of classification tree analysis. *BMC Pediatr* 2018;18(1):109. DOI: 10.1186/s12887-018-1078-y.
24. Méndez A, González G. Dengue haemorrhagic fever in children: ten years of clinical experience. *Biomedica* 2003;23(2):180–193. DOI: 10.7705/biomedica.v23i2.1210English abstract.
25. Laoprasopwattana K, Pruekprasert P, Dissaneewate P, et al. Outcome of dengue hemorrhagic fever-caused acute kidney injury in Thai children. *J Pediatr* 2010;157(2):303–309. DOI: 10.1016/j.jpeds.2010.02.008.
26. Mehra N, Patel A, Abraham G, et al. Acute kidney injury in dengue fever using acute kidney injury network criteria: incidence and risk factors. *Trop Doct* 2012;42(3):160–162. DOI: 10.1258/td.2012.120023.

27. Mallhi TH, Khan AH, Adnan AS, et al. Incidence, characteristics and risk factors of acute kidney injury among dengue patients: a retrospective analysis. *PLoS ONE* 2015;10(9):e0138465. DOI: 10.1371/journal.pone.0138465.
28. Khali MAM, Sarwar S, Chaudry MA, et al. Acute kidney injury in dengue virus infection. *Clin Kidney J* 2012;5(5):390–394. DOI: 10.1093/ckj/sfs117.
29. Wiwanitkit V. Acute renal failure in the fatal cases of dengue hemorrhagic fever, a summary in thai death cases. *Ren Fail* 2005;27(5):647. DOI: 10.1080/08860220500200916.
30. Lee IK, Liu JW, Yang KD. Clinical characteristics, risk factors, and outcomes in adults experiencing dengue hemorrhagic fever complicated with acute renal failure. *Am J Trop Med Hyg* 2009;80(4):651–655. DOI: 10.4269/ajtmh.2009.80.651.
31. Lim CTS, Fuah KW, Lee SE, et al. Dengue-associated acute kidney infection: an updated and comprehensive qualitative review of literature. *EMJ Nephrol* 2019;7:86–94.
32. Kuo MC, Lu PL, Chang JM, et al. Impact of renal failure on the outcome of dengue viral infection. *Clin J Am Soc Nephrol* 2008;3(5):1350–1356. DOI: 10.2215/CJN.00020108.
33. Mehra N, Saha A, Dubey NK, et al. Acute tubular necrosis in dengue fever in a child. *Indian J Nephrol* 2012;22(5):400–401. DOI: 10.4103/0971-4065.103917.
34. Macedo E. Urine output assessment as a clinical quality measure. *Nephron* 2015;131(4):252–254. DOI: 10.1159/000437312.
35. Levin M, Cunningham AJ, Wilson C, et al. Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial. *Lancet Respir Med* 2019;7(7):581–593. DOI: 10.1016/S2213-2600(19)30114-6.
36. Ranjit S, Ramanathan G, Ramakrishnan B, et al. Targeted interventions in critically ill children with severe dengue. *Indian J Crit Care Med* 2018;22(3):154–161. DOI: 10.4103/ijccm.IJCCM\_413\_17.
37. Gan VC. Dengue: Moving from current standard of care to state-of-the-art treatment. *Curr Treat Options Infect Dis* 2014;6(3):208–226. DOI: 10.1007/s40506-014-0025-1.
38. Biswas A, Devgan V, Pangtey G, et al. National guidelines for clinical management of dengue fever. 2014;5:23–28.
39. Raina R, Sethi SK, Wadhvani N, et al. Fluid overload in critically ill children. *Front Pediatr* 2018;6:306. DOI: 10.3389/fped.2018.00306.
40. Mishra A, Singh VK, Nanda S. Rhabdomyolysis and acute kidney injury in dengue fever. *BMJ Case Rep* 2015;2015:bcr2014209074. DOI: 10.1136/bcr-2014-209074.
41. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med* 2009;361(1):62–72. DOI: 10.1056/NEJMra0801327.
42. Oliveira JFP, Burdmann EA. Dengue-associated AKI. *Clin Kidney J* 2015;8(6):681–685. DOI: 10.1093/ckj/sfv106.
43. Krzych ŁJ, Czempik PF. Impact of furosemide on mortality and the requirement for renal replacement therapy in acute kidney injury: a systematic review and meta-analysis of randomised trials. *Ann Intensive Care* 2019;9(1):85. DOI: 10.1186/s13613-019-0557-0.
44. Selewski DT, Goldstein SL. The role of fluid overload in the prediction of outcome in acute kidney injury. *Pediatr Nephrol* 2018;33(1):13–24. DOI: 10.1007/s00467-016-3539-6.
45. Diptyanusa A, Phumratanaprapin W, Phonrat B, et al. Characteristics and associated factors of acute kidney injury among adult dengue patients: a retrospective single-center study. *PLoS ONE* 2019;14(1):e0210360. DOI: 10.1371/journal.pone.0210360.
46. Naqvi R. Dengue infection causing acute kidney injury. *Trop Med Surg* 2016;4(02):211. DOI: 10.4172/2329-9088.1000211.
47. Patel ML, Himanshu D, Chaudhary SC, et al. Clinical characteristic and risk factors of acute kidney injury among dengue viral infections in adults: a retrospective analysis. *Indian J Nephrol* 2019;29(6):15–21. DOI: 10.4103/ijn.IJN\_437\_17.
48. Mallhi TH, Khan AH, Adnan AS, et al. Short-term renal outcomes following acute kidney injury among dengue patients: A follow-up analysis from large prospective cohort. *PLoS ONE* 2018;13(2):e0192510. DOI: 10.1371/journal.pone.0192510.
49. Hsu RK, Hsu CY. The role of acute kidney injury in chronic kidney disease. *Semin Nephrol* 2016;36(4):283–292. DOI: 10.1016/j.semnephrol.2016.05.005.
50. Sigurjonsdottir VK, Chaturvedi S, Mammen C, et al. Pediatric acute kidney injury and the subsequent risk for chronic kidney disease: is there cause for alarm? *Pediatr Nephrol* 2018;33(11):2047–2055. DOI: 10.1007/s00467-017-3870-6.
51. Lima EQ, Nogueira ML. Viral hemorrhagic fever-induced acute kidney injury. *Semin Nephrol* 2008;28(4):409–415. DOI: 10.1016/j.semnephrol.2008.04.009.