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Dengue Induced Nephropathies

Amer Hayat Khan[1]* and Tauqeer Hussain Mallhi[1]

[1]School of Pharmaceutical Sciences, University Sains Malaysia, Malaysia

***Corresponding author:** Amer Hayat Khan, Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800, Penang, Malaysia, Email: dramer2006@gmail.com

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DENGUE

Dengue Fever (**DF**) and its severe forms- Dengue Hemorrhagic Fever (**DHF**) and Dengue Shock Syndrome (**DSS**)- have become major international public health concerns. Over the past three decades, there has been a dramatic global increase in the frequency of Dengue Fever (**DF**), DHF and DSS and their epidemics, with a concomitant increase in disease incidence Dengue is found in tropical and subtropical regions around the world, predominantly in urban and semi-urban areas (Figure 1). The disease is caused by a virus belonging to family Flaviviradae that is spread by Aedes (Stegomyia) mosquitoes. There is no specific treatment for dengue, but appropriate medical care frequently saves the lives of patients with the more serious dengue hemorrhagic fever. The most effective way to prevent dengue virus transmission is to combat the disease-carrying mosquitoes [1-2].

Some Important Key Facts about Dengue

- About 2.5 billion people – two fifths of the world's population in tropical and subtropical countries – are at risk.
- An estimated 50 million dengue infections occur worldwide annually.
- An estimated 500,000 people with DHF require hospitalization each year. A very large proportion (approximately 90%) of them are children aged less than five years, and about 2.5% of those affected die.
- Dengue and DHF is endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. The South-East Asia and Western Pacific regions are the most seriously affected.
- Epidemics of dengue are increasing in frequency. During epidemics, infection rates among those who have not been previously exposed to the virus are often 40% to 50% but can also reach 80% to 90%.
- Seasonal variation is observed.
- Aedes (Stegomyia) aegypti is the primary epidemic vector.
- Primarily an urban disease, dengue and DHF are now spreading to rural areas worldwide.
- Imported cases are common.
- Co-circulation of multiple serotypes/genotypes is evident.

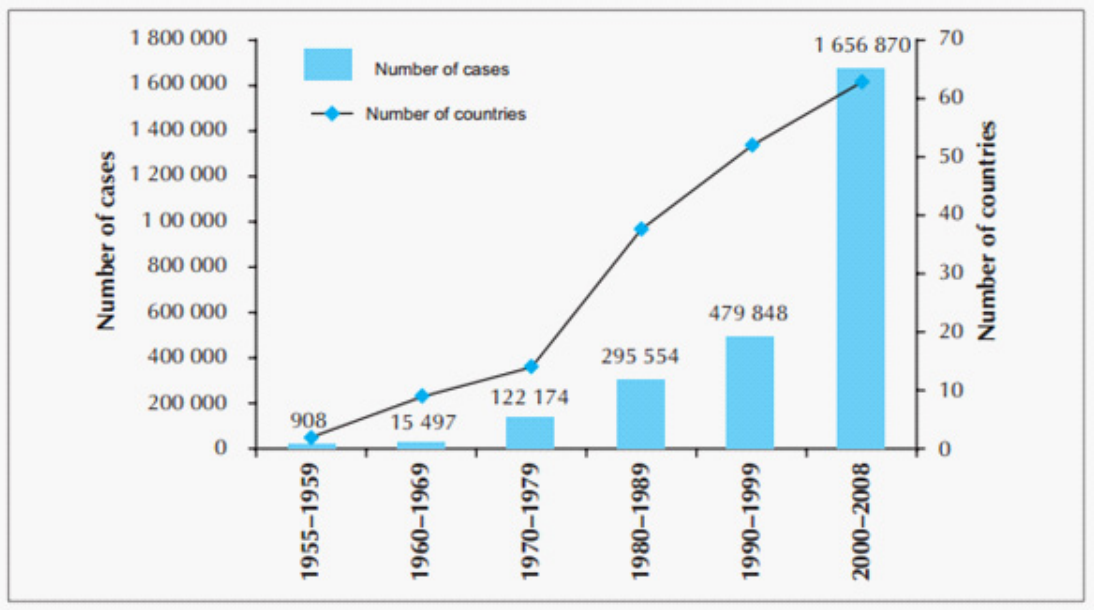

Figure 1: Average annual number of cases of DF/DHF reported to WHO.

DENGUE CASE DEFINITION

In 1997 the dengue case definition was imitated in terms of its complexity and applicability. This recognition of the limitations led to a multicenter study in seven countries in Asia and Latin America and a new case definition emerged from this study. The new WHO classification for dengue severity is divided into Dengue without Warning Signs, Dengue with Warning Signs, and Severe Dengue. In 2009, new dengue case definitions were evolved as given below [3].

Dengue without warning signs

- Fever and 2 of the following:
- Nausea/vomiting
- Rash
- Aches and pains
- Leukopenia
- Positive tourniquet test.

Dengue with warning signs

- Dengue (as defined above) with any of the following:
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation (e.g., ascites, pleural effusion)
- Mucosal bleeding
- Lethargy/restlessness
- Liver enlargement >2 cm
- Laboratory: increase in haematocrit concurrent with rapid decrease in platelet count.
- Warning signs require strict observation and medical intervention.

Severe dengue

- Dengue with at least 1 of the following:
- Severe plasma leakage leading to shock (dengue shock syndrome) or fluid accumulation with respiratory distress
- Severe bleeding (as evaluated by a clinician)
- Severe organ involvement (i.e., AST or ALT 1000 or greater, impaired consciousness, organ failure).

- More recently in 2011, Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever has been issued by WHO regional office for South East Asia (**WHO-SEARO**). According to these guidelines, dengue viral infection was categorized into **DF**, **DHF** and **DSS** with sub-categorization of **DHF** as given below in Figure 2 [1].

DF/ DHF	Grade	Signs and Symptoms	Laboratory
DF		Fever with two of the following: • Headache. • Retro-orbital pain. • Myalgia. • Arthtralgia/bone pain. • Rash. • Haemorrhagic manifestations. • **No evidence of plasma leakage**.	• Leucopenia (wbc ≤5000 cells/mm³). • Thrombocytopenia (Platelet count <150 000 cells/mm³). • Rising haematocrit (5% – 10%). • No evidence of plasma loss.
DHF	I	Fever and haemorrhagic manifestation (positive tourniquet test) and **evidence of plasma leakage**	Thrombocytopenia <100 000 cells/ mm³; HCT rise ≥20%
DHF	II	As in Grade **I plus** spontaneous bleeding.	Thrombocytopenia <100 000 cells/mm³; HCT rise ≥20%.
DHF*	III	As in Grade **I or II plus** circulatory failure (weak pulse, narrow pulse pressure (≤20 mmHg), hypotension, restlessness).	Thrombocytopenia <100 000 cells/mm³; HCT rise ≥20%.
DHF*	IV	As in Grade **III** plus profound shock with undetectable BP and pulse	Thrombocytopenia < 100 000 cells/mm³; HCT rise ≥20%.

Figure 2: WHO classification of dengue infections and grading of severity of **DHF [1].**

EXPANDED DENGUE SYNDROME (UNUSUAL OR ATYPICAL MANIFESTATIONS

Unusual manifestations are uncommon. In recent years with the geographical spread of dengue illness and with more involvement of adults, there have been increasing reports of **DF** and **DHF** with unusual manifestations. These include: neurological, hepatic, renal and other isolated organ involvement. These could be explained as complications of severe profound shock or associated with underlying host conditions/diseases or co-infections. Central nervous system (**CNS**) manifestations including convulsions, spasticity, changes in consciousness and transient paresis have been observed. The underlying causes depend on the timing of these manifestations in relation to the viremia, plasma leakage or convalescence. Encephalopathy in fatal cases has been reported in Indonesia, Malaysia, Myanmar, India and Puerto Rico. However, in most cases there have been no autopsies to rule out bleeding or occlusion of the blood vessels. Although limited, there is some evidence that on rare occasions dengue viruses may cross the blood-brain barrier and cause encephalitis. It should be noted that exclusion of concurrent infections has not been exhaustive. Table 1 details the unusual/atypical manifestations of dengue. The above-mentioned unusual manifestations may be underreported or unrecognized or not related to

dengue. However, it is essential that proper clinical assessment is carried out for appropriate management, and causal studies should be done [1,4,5]. The following host factors contribute to more severe disease and its complications:

- Infants and the elderly
- Obesity
- Pregnant women
- Peptic ulcer disease
- Women who have menstruation or abnormal vaginal bleeding,
- Haemolytic diseases such as glucose-6-phosphatase dehydrogenase (G-6PD) deficiency, thalassemia and other haemoglobinopathies,
- Congenital heart disease,
- Chronic diseases such as diabetes mellitus, hypertension, asthma, ischemic heart disease, chronic renal failure, liver cirrhosis,
- Patients on steroid or NSAID treatment and others.

Table 1: Expanded dengue syndrome (Unusual or atypical manifestations of dengue).

System	Unusual or atypical manifestations
Neurological	Febrile seizures in young children. Encephalopathy. Encephalitis/aseptic meningitis. Intracranial haemorrhages/thrombosis. Subdural effusions. Mononeuropathies/polyneuropathies/Guillane-Barre Syndrome. Transverse myelitis.
Gastrointestinal/hepatic	Hepatitis/fulminant hepatic failure. Acalculous cholecystitis. Acute pancreatitis. Hyperplasia of Peyer's patches. Acute parotitis.
Renal	Acute renal failure. Hemolytic uremic syndrome.
Cardiac	Conduction abnormalities. Myocarditis. Pericarditis.
Respiratory	Acute respiratory distress syndrome. Pulmonary haemorrhage.
Musculoskeletal	Myositis with raised creatine phosphokinase (CPK). Rhabdomyolysis.
Lymphoreticular/bone marrow	Infection associated haemophagocytic syndrome. IAHS or Haemophagocytic lymphohistiocytosis (HLH), idiopathic thrombocytopenic purura (ITP). Spontaneous splenic rupture. Lymph node infarction.
Eye	Macular haemorrhage. Impaired visual acuity. Optic neuritis.
Others	Post-infectious fatigue syndrome, depression, hallucinations, psychosis, alopecia.

DENGUE INDUCED NEPHROPATHIES

Among all atypical manifestations of dengue infection, renal disorders are neglected and least studied complications. Spectrum of dengue associated renal involvements varies from mild glomerulonephritis, urinary sedimentations to severe hemolytic-uremic syndrome (may lead to permanent visual impairment) and Acute Kidney Injury (**AKI**) [6].

Proteinuria

Proteinuria has been detected in as high as 74% of patients with **DHF**. During a dengue-3 epidemic in Queensland, Australia, Horvath et al. recorded Proteinuria in 74% of patient in whom urinalysis was performed. In this cohort, one patient had 10.8 g/day Proteinuria and was diagnosed with the nephrotic syndrome. Vasanwala and colleagues reported two **DHF** patients with nephrotic-range Proteinuria [7]. Daily protein excretion was 8.1 g/day and 9.0 g/day based on a random urine protein to creatinine ratio. These patients did not have hematuria or elevated serum creatinine concentrations. Garcia et al. retrospectively studied 74 patients with dengue fever or **DHF** who had a platelet count of less than 125,000/mm3. The prevalence of Proteinuria in this cohort was 30% [8].

Hutspardol and coworkers reported a 9-year-old boy with no significant medical history who presented with a 4-day history of high-grade fever, headache, diarrhea, hepatomegaly, and azotemia [9]. A diagnosis of dengue infection was suggested by a positive tourniquet test and confirmed when dengue IgM antibodies were detected. Daily urinary protein excretion was 3.4 g/day based on a random urine protein to creatinine ratio. Renal biopsy was not performed. Supportive care was provided and the patient's condition improved. One month following discharge from the hospital, urinary protein excretion was normal.

Glomerulonephritis

Various types of glomerulonephritis have been reported during or shortly after dengue infection in humans and mouse models of dengue infection.

Barreto et al, infected mice with dengue virus type 2 [10]. Forty-eight hours later, glomerular enlargement, increased end capillary and mesangial cellularity as well as glomerular IgM deposition were noted. Similarly, Boonpucknavig and colleagues examined mice with dengue virus type 2 infections [11]. By the third week of infection, immune-complex deposition and proliferative lesions were evident in the glomeruli.

Hematuria has been reported in up to 12.5% of patients with DHF by Futrakul et al. [12]. Boonpucknavig and colleagues observed glomerular IgG, IgM, and C3 deposition in 10 of 20 patients (50%) with DHF and renal disease [13]. Ultra structural examination demonstrated glomerular immune complex type deposits associated with mesangial cell hypertrophy. In addition, dense spherical particles 40-50 nm in diameter was found in 12 cases (60%). In the patients with renal disease and glomerular immunoreactions, renal biopsy was performed during the second week

following the onset of fever. To localize viral antigen, Jessie et al. examined tissues obtained from patients whose dengue infection was confirmed serologically or virologically [14]. Dengue antigen was detected in the renal tubular epithelial cells in 3 of 8 cases (37.5%).

A recent case report describes deranged renal function and hematuria in a 3-year-old boy with DHF [15]. The patient also had fever, vomiting, hypertension, and Oliguria. However, he did not have shock, sepsis, hemolytic, or rhabdomyolysis. Urinalysis demonstrated red blood cells and granular casts. Complement C3 level was reduced. The authors argued that the patient had glomerulonephritis. However, renal biopsy was not available. The patient recovered with supportive care.

Lizzaraga and Nayer encountered a case of 66-year-old woman from Honduras who was diagnosed with acute dengue infection and rapidly progressive glomerulonephritis. A diagnosis of dengue infection was based on the clinical ground and an elevated dengue IgM titer. Renal biopsy revealed severe crescentic glomerulonephritis. Immunofluorescence examination demonstrated strong linear IgG deposition along glomerular capillary walls. Serologic tests demonstrated antibodies against GBM, MPO, and platelet glycoproteins. The patient was diagnosed with anti-GBM disease associated with ANCA with MPO specificity. Despite heavy immunosuppressant and Plasmapheresis, IgG titers against dengue virus continued to rise confirming the diagnosis of acute dengue infection [16].

IgA Nephropathy

Upadhyay and colleagues reported a 15-year-old boy who was diagnosed with dengue infection and ARF necessitating renal replacement therapy [17]. Urinalysis showed hematuria and Proteinuria. Renal biopsy demonstrated mesangial proliferation and IgA deposition consistent with IgA nephropathy as well as acute tubular necrosis. Resolution of mesangial proliferation and IgA deposition was documented on renal biopsy six weeks later.

Lupus Nephritis

A case of dengue infection evolving into systemic lupus Erythematosus and lupus nephritis has been reported. Rajadhyaksha et al. reported a 22-year-old woman who presented with high-grade fever, skin rash, shortness of breath, retro-orbital pain, abdominal pain, arthralgia, and myalgia [18]. She was diagnosed with dengue infection on the clinical ground and elevated dengue IgM titers. At the time, serum creatinine concentration was 1.0 mg/dL. Supportive care was provided and the patient was discharged home. Four weeks later, she developed fever, arthralgia, rash, and anasarca. Serum creatinine concentration was 5.0 mg/dL. Urinalysis revealed proteinuria and hematuria. Daily urinary protein excretion was 6.3 g/day based on a 24-hour urine collection. Antibodies directed against nuclear antigens including ANA and double-stranded DNA were detected. Complements C3 and C4 were reduced. Renal biopsy showed diffuse proliferative glomerulonephritis consistent with lupus nephritis.

Hemolytic Uremic Syndrome

Dengue fever-induced hemolytic uremic syndrome, characterized by a triad consisting of hemolytic anemia, thrombocytopenia and AKI, has been described in three patients. One of the cases was subjected to a renal biopsy, which showed thrombotic microangiopathy with arteriolar and glomerular micro thrombi, and electronic microscopy revealed the presence of microtubuloreticular structures, suggesting a viral infection. All three patients survived with recovery of renal function [16].

Acute Kidney Injury (AKI) or Acute Renal Failure (ARF)

Acute Kidney Injury (**AKI**) is a potential complication of severe dengue infection and is typically associated with hypotension, rhabdomyolysis, or hemolysis [19]. The prevalence of **AKI,** varies from study to study depending upon population and criteria used to define **AKI,** is 1.6% among 617 children with **DHF** in Colombia, 3.3% in hospitalized adults with **DHF**, 4.9% in 81 Chinese patients with **DHF**/**DSS**, and 5% in **DHF** patients in Qatar [20].

The development of **ARF** in patients with dengue infection is associated with increased mortality [21]. In Thailand, the prevalence of **ARF** in fatal **DHF** was 33.3%, compared with 0.3% in all **DHF** cases [22]. In a retrospective series, 60% of hospitalized **DHF** patients with **ARF** died. **DHF** patients with **ARF** were predominantly older men and had other co morbidities. Multivariate analysis showed that **DSS** was an independent risk factor for the development of **ARF** in patients with **DHF**. More recently, Mallhi et al reported **AKI** among 14.2% of dengue population in Malaysia, a tropical country with worst dengue crisis [6]. Summary of the some cases of dengue having **AKI** with their proposed mechanism of injury are given below in Table 2. Nephropathies other than AKI are demonstrated in Table 3.

Table 2: Summary of dengue cases having AKI with proposed mechanisms of AKI.

Cases	Age, gender	Severity of dengue	Days of illness before admission	Proposed mechanism of AKI	Hospital stay (Days)	Outcome
1	28-year M	DF	20	Rhabdomyolosis induced ATN	21	Recover
2	48-year M	DF	NR	Hemolytic uremic syndrome	NR	Recover
3	66-year M	DSS	5	Severe Rhabdomyolosis	47	Death
4	33-year M	DF	5	Rhabdomyolosis	4	Recover
5	33-year M	DHF	NR	Rhabdomyolosis	2	Death
6	42-year M	DF	5	Rhabdomyolosis	9	Recover
7	13-year M	DF	14	Invasion of virus into kidneys	7	Recover
8	48-year F	DHF	8	Invasion of virus into kidneys	17	Recover
9	30-year M	DF	6	Deposition of immune complex	35	Recover
10	40-year M	DF	4	Rhabdomyolosis and myositis	NR	Recover
11	8-year M	DF	5	Invasion of virus into kidneys	NR	Recover

NR: not reported, M: male, F: Female

Source: Mallhi TH, Sarriff A, Adnan AS, Khan YH, Hamzah AA, Jummaat F, Khan AH. Dengue-induced Acute Kidney Injury (DAKI): A Neglected and Fatal Complication of Dengue Viral Infection-A Systematic Review. Journal of the College of Physicians and Surgeons Pakistan. 2015b Nov; 25(11):828-34.

Table 3: Summary of case reports demonstrating nephropathies other than AKI among dengue patients.

Cases	age, gender	Severity of dengue	Renal disease(s)	Illness days before admission	Proposed mechanism of renal disease	Hospital stay (Days)	Outcome
1	4-year M	DF	Glomerulonephritis	5	Mild proliferation of mesangial cells, IgG, C3, IgM deposition in glomerulus	21	Recover
2	32-year M	DHF	Nephrotic range proteinuria	5	Autoimmune mechanism	12	Recover
	42-year M	DHF	Nephrotic range proteinuria	6	Autoimmune mechanism	10	Recover
3	9-year M	DHF	Nephrotic range proteinuria	4	IgG, IgM, C3 localization of glomeruli	20	Recover
4	22-year F	DF	Systemic lupus erythmatosis & lupus nephritis	10	Dysfunctional immune response causing autoimmuneity	NR	Recover
5	15-year M	DF	IgA nephropathy/ mesangioproliferative glomerulonephritis	7	IgA immune response to viral antigens lead to nephritogenic circulating immune complexes	35	Recover
6	11-year M	DHF	Glomerulonephritis	6	Immune complex deposition in mesangium of glomerulus	12	Recover

M: male, F: female, DF: dengue fever, DHF: dengue hemorrhagic fever, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, C3: complement component 3, NR: not reported

Source: Mallhi TH, Sarriff A, Adnan AS, Khan YH, Hamzah AA, Jummaat F, Khan AH. Dengue-induced Acute Kidney Injury (DAKI): A Neglected and Fatal Complication of Dengue Viral Infection-A Systematic Review. Journal of the College of Physicians and Surgeons Pakistan. 2015b Nov; 25(11):828-34.

DENGUE ASSOCIATED ACUTE KIDNEY INJURY

AKI is a significant, albeit poorly studied, complication of dengue. The data available are heterogeneous and mostly originate from retrospective case series and case reports. The reported frequency of this association exhibits wide variation in accordance to the particular population being assessed, severity of dengue, criteria used for the diagnosis of **AKI** and time of evaluation. Laoprasopwattana et al. [23] reported an incidence of 0.9% among children in Thailand, and Lee et al. [24] reported an incidence of 3.3% among adults in Taiwan. In a Brazilian intensive care unit for infectious diseases, dengue was the cause of 4% of the cases of **AKI** diagnosed using the risk, injury, failure, loss of kidney function and end-stage acute kidney disease (**RIFLE**) criteria [25]. In a more recent study that employed the Acute Kidney Injury Network (**AKIN**) criteria for diagnosis, the incidence of AKI was 10.8% [26]. Using the **AKIN** criteria in a retrospective analysis, Khalilet al. [27] identified **AKI** in 13.3% of a series of patients with dengue confirmed by the presence of IgM antibodies, independent of the severity of disease; 64.8% of the patients were in Stage 1, 18.3% Stage 2 and 16.9% Stage 3 of the disease. In another study, the **RIFLE** classification was used to investigate the occurrence of AKI in patients with tropical acute febrile disease. The results showed that the incidence of **AKI** among patients with dengue upon admission to the hospital was 35.7%.

More recently Mallhi et al reported higher incidence of **AKI** (14.2%) among dengue patients with mortality rate of 1.2% [6]. Mallhi et al also described those patients with **AKI** before admission to hospital had higher risks of death than the patients who evolved **AKI** during their hospital stay. Similarly, patients in whom **AKI** progressed to severe stage are more likely to die than patients with non-progressive **AKI** [21]. Mallhi et al., also tried to compare incidence and characteristics of dengue induced **AKI** by using different definitions to define **AKI** [20].

Criteria to Define AKI

Currently three Criteria are being used to classify **AKI** in clinical practice (27). Acute kidney injury **(AKI),** formerly called acute renal failure (**ARF**), is commonly defined as an abrupt decline in renal function, clinically manifesting as a reversible acute increase in nitrogen waste products-measured by blood urea nitrogen **(BUN)** and serum creatinine levels-over the course of hours to weeks. The vague nature of this definition has historically made it difficult to compare between scholarly works and to generalize findings on epidemiologic studies of **AKI** to patient populations. Several classification systems have been developed to streamline research and clinical practice with respect to **AKI**.

In 2002, the Acute Dialysis Quality Initiative (ADQI) was created with the primary goal of developing consensus and evidence-based guidelines for the treatment and prevention of acute kidney injury (AKI). The first order of business was to create a uniform, accepted definition of AKI; hence, the RIFLE criteria were born (see the table below). RIFLE is an acronym of Risk, Injury, and Failure; and Loss; and End-stage kidney disease. Table 4, RIFLE Classification System for Acute Kidney Injury.

Table 4: RIFLE classification system to stratify **AKI.**

Stage	GFR Criteria	UO Criteria
Risk	Scr increased 1.5-2 times baseline or GFR decreased >25%	UO < 0.5 mL/kg/h < 6 h
Injury	SCr increased 2-3 times baseline or GFR decreased >50%	UO < 0.5 mL/kg/h >12 h
Failure	SCr increased >3 times baseline or GFR decreased 75% or SCr ≥4 mg/dL; acute rise ≥0.5 mg/dL	UO < 0.3 mL/kg/h 24 h (oliguria) or anuria 12 h
Loss of function	Persistent acute renal failure: complete loss of kidney function >4 wk (requiring dialysis)	
ESRD[d]	Complete loss of kidney function >3 mo (requiring dialysis)	

GFR = Glomerular filtration rate.
UO = Urine output.
SCr = Serum creatinine.
ESRD = end-stage renal disease.

Note: Patients can be classified either by GFR criteria or by UO criteria. The criteria that support the most severe classification should be used. The superimposition of acute on chronic failure is indicated with the designation RIFLE-F_C; failure is present in such cases even if the increase in SCr is less than 3-fold, provided that the new SCr is greater than 4 mg/dL (350 µmol/L) and results from an acute increase of at least 0.5 mg/dL (44 µmol/L).

When the failure classification is achieved by UO criteria, the designation of RIFLE-F_O is used to denote oliguria. The initial stage, "risk," has high sensitivity; more patients are classified in this mild category, including some who do not actually have renal failure. Progression through the increasingly severe stages of RIFLE is marked by decreasing sensitivity and increasing specificity.

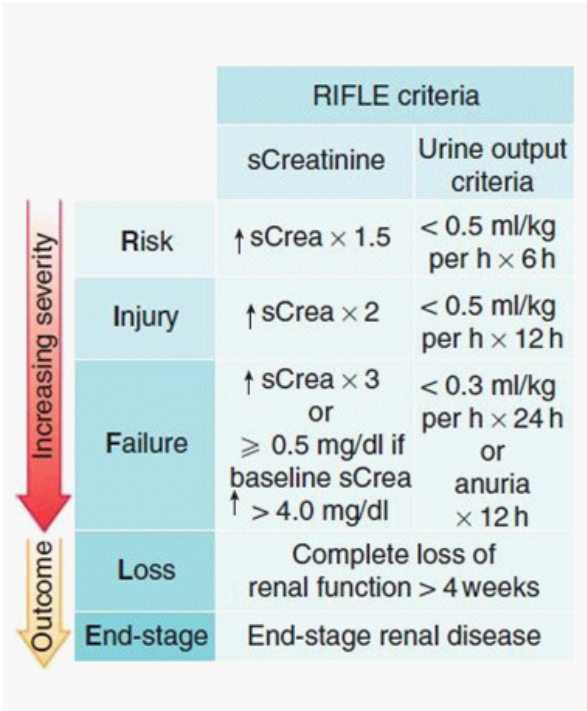

Figure 3: RIFLE serum creatinine and Urine output criteria according to severity and outcome stages.

In September 2004, the Acute Kidney Injury Network (**AKIN**) was formed. **AKIN** advised that the term acute kidney injury (**AKI**) be used to represent the full spectrum of renal injury, from mild to severe, with the latter having increased likelihood for unfavorable outcomes (eg, loss of function and end-stage renal disease [**ESRD**]). A report by the AKIN proposed the following criteria for **AKI** (Figure 4).

- Abrupt (within 48 h) reduction in kidney function currently defined as an absolute increase in serum creatinine of 0.3 mg/dL or more (≥26.4 μmol/L) or
- A percentage increase in serum creatinine of 50% or more (1.5-fold from baseline) or
- A reduction in urine output (documented oliguria of < 0.5 mL/kg/h for >6 h)

The **AKIN** criteria differ from the **RIFLE** criteria in several ways. The RIFLE criteria are defined as changes within 7 days, while the **AKIN** criteria suggest using 48 hours. The **AKIN** classification includes less severe injury in the criteria and **AKIN** also avoids using the glomerular filtration rate as a marker in **AKI**, as there is no dependable way to measure glomerular filtration rate and estimated glomerular filtration rate are unreliable in **AKI**.

AKIN notes that the diagnostic criteria proposed only after volume status has been optimized and urinary tract obstructions must be excluded when using oliguria as diagnostic criteria.

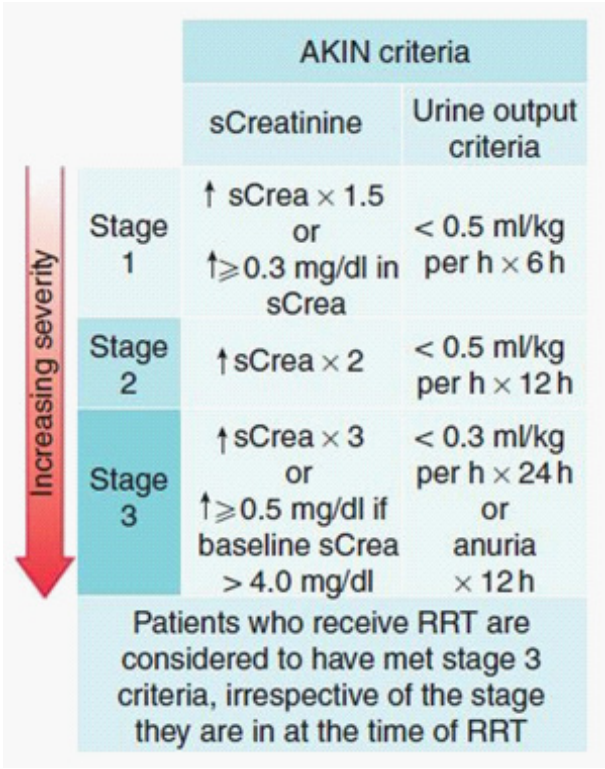

Figure 4: AKIN serum creatinine and urine output criteria to stratify AKI.

In 2012 the Kidney Disease Improving Global Outcomes (**KDIGO**) released their clinical practice guidelines for acute kidney injury (AKI), which build off of the RIFLE criteria and the **AKIN** criteria.

KDIGO defines AKI as any of the following:

- Increase in serum creatinine by 0.3mg/dL or more within 48 hours or
- Increase in serum creatinine to 1.5 times baseline or more within the last 7 days or
- Urine output less than 0.5 mL/kg/h for 6 hours

The KDIGO has also recommended a staging system for the severity of the AKI. The KDIGO consensus classification has yet to be validated.

Table 5: KDIGO staging for AKI severity.

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline or ≥0.3 mg/dL increase	< 0.5 mL/kg/h for 6 h
2	2-2.9 times baseline	< 0.5 mL/kg/h for 12 h
3	3 times baseline or Increase in serum creatinine to ≥4 mg/dL or Initiation of renal replacement therapy	< 0.3 mL/kg/h for 24 h or Anuria for ≥12 h

Criteria to Define AKI in Dengue

In most of the studies conducted to evaluate AKI among dengue patients, AKI was classified as rapid elevation of serum creatinine levels above 2mg/dL (176.8 μmol/L). By this criterion, mild to moderate cases of AKI might be ignored. It might be a reason that studies using such criteria has very low occurrence (0.9% and 3.3%) of **AKI** among their dengue cohort [23, 24]. Studies using **AKIN** criterion showed high prevalence of **AKI** among dengue patients as showed in Table 6.

Table 6: Summary of studies comparing dengue patients with and without AKI by using different classification system.

Author`s name	Study population	Demographics (n, age, gender)	Severity of dengue	AKI definition	Incidence of AKI	Longer hospitalization (AKI vs Non-AKI)	Mortality (AKI vs non AKI)
Mallhi et al[6] (Retrospective)	Patients >12 years of age	667, mean age 0.68 ± 16.13 years	DVI	AKIN	14.2%	65.3% vs 48.3%	8.4% vs 0%
Mehra et al[26] (Retrospective)	Patients of all age groups	223, 130 males, mean age 26.2 ± 18.2 years	DVI	AKIN	10.8%	NR	Overall: 9%*
Khalil et al[28] (Retrospective)	Patients of all age groups	532, 377 males, mean age 35.2 ± 14.7 years	DVI	AKIN	13.3%	59.2% vs 22.6%	11.3% vs 0%
Laoprasopwattana et al[23] (Retrospective)	Children <15 years with	75, mean age 9.1 ± 3.6 years, 37 males	DHF/DSS	SCr > 2 mg/dL	0.9 %	NR	64% vs 0%
Lee et al[22] (Retrospective)	Patients of all age groups	304, 139 males, age range 19-88 years	DHF	SCr > 2 mg/dL	3.3 %	NR	60% vs 0%
Lee et al[24] (Retrospective)	Patients of all age groups	307, 139 males, age range 37-74 years	DHF	SCr > 2 mg/dL	3.9 %	NR	NR

n: represents number of patients enrolled in study, DVI: dengue viral infection including all severities (DF, DHF, DSS), AKI: acute kidney injury, AKIN: Acute Kidney Injury Network classification, AKIN-1,2,3: represents three severity stages of AKIN network classification, DHF: dengue hemorrhagic fever, DSS: dengue shock syndrome, SCr: serum creatinine, mg/dL: milligram per deciliter, NR: not reported

*subjected to overall mortality reported in study while author stated that higher mortality was observed among patients with AKI

Source: Mallhi TH, Sarriff A, Adnan AS, Khan YH, Hamzah AA, Jummaat F, Khan AH. Dengue-induced Acute Kidney Injury (DAKI): A Neglected and Fatal Complication of Dengue Viral Infection-A Systematic Review. Journal of the College of Physicians and Surgeons Pakistan. 2015b Nov; 25(11): 828-34.

Acute Kidney Injury Network (AKIN) and conventional definition (SCr >2mg/dL) were two criteria used to stratify dengue patients into AKI in studies described in Table 6.The use of conventional definition was subjected to lower incidence (0.9% to 3.9%) of AKI. It can be explained by the reason that conventional definition classifies only severe cases of AKI with serum creatinine (SCr) levels greater than 2 mg/dL. On the other hand, AKIN criteria was found to be more sensitive and studies using same criteria demonstrated higher incidence of AKI in dengue infection. AKIN classify patients into AKI with 1.5 times increase in SCr from baseline within 7 days or with increased Scr ≥26.2 μmol/L from baseline within 48 hours. Similarly, RIFLE classification (Risk, Injury, Failure, Loss of function and End stage renal disease) is comparable to **AKIN** criteria and can be used to classify AKI. We did not come across any study using **RIFLE** criteria to define AKI among dengue patients. However, Kuo et al29 and Basu et al30 reported very high incidence of **DAKI** by using **RIFLE** criteria (27.1% and 35.7% respectively). It is due to very less number of dengue patients (28 patients) 30 and selection biasness of dengue cases (as out of total studied participants, **RIFLE** criteria were validated in half of the patients). 29 These findings suggest that there is a need to develop consensus on definition of **AKI** among dengue patients in order to determine true incidence. Additionally, use of different definitions not only causes great disparity in incidence but also variations in clinico-laboratory characteristics that make it difficult or even impossible to compare studies.

Risk Factors of AKI in Dengue patients

Prior knowledge of expected clinical profile and predictors of **AKI** development would provide information to identify individuals at higher risk and on the other hand, give sufficient time to clinicians for reducing associated morbidity and mortality. Several risk factors were identified for the development of **AKI** during dengue course as demonstrated in Table 7. Severe dengue, sepsis, neurological involvements, male gender and old age are well known predictors of dengue induced **AKI**. Similarly, patients with co-infections, concurrent bacteremia, co-existing viral hepatitis and co-morbidities had higher odds of developing **AKI** than patients without co morbidities and co-infections. However, good predictors of **AKI** in dengue infection are presently lacking with current research. Biomarkers of **AKI** that are capable of early detection, risk stratification, and prognostication would represent a tremendous advance in the care of patients with **DAKI**. Neutrophil Gelatinase-Associated Lipocalin (**NGAL**), Kidney Injury Molecule-1 (**KIM**-1), Liver-type Fatty Acid Binding Protein (L-FABP), Interleukin-18 (IL-18) and NF-κB are some novel AKI biomarkers that provide early and specific diagnosis of AKI with good predictive ability of clinical outcomes 41,42, though the value of these biomarkers have not studied in dengue patients. These findings suggest the need of more clinical studies with much larger patient`s pool in order to get accurate and robust predictive model of dengue induced AKI [31, 32].

Table 7: Summary of studies identifying the risk factors/predictors of acute kidney injury among dengue patients.

Authors name	Risk Factors/Predictors of AKI in dengue
Mehra et al [26]	Elevated levels of ALT and ALP Low levels of albumin and serum HCO_3 Co-existing viral hepatitis Sepsis Multiple organ dysfunctions (MODs) Need for inotropes with or without hypotension
Khalil et al [28]	Male gender Presence of sever dengue (DHF/DSS) Neurological involvements Prolongation of aPTT
Laoprasopwattana et al [23]	DHF grade IV (DSS) Obesity
Lee et al [22]	Age >30 years Co-morbidities (previous shock, chronic kidney disease) GIT bleeding Concurrent bacteremia
Mallhi et al [6]	Male gender Diabetes mellitus Dengue hemorrhagic fever (DHF) Multiple organ failure (MOF) Delayed hospitalization

ALT: alanine aminotransferase, ALP: alkaline phosphatase, HCO_3: bicarbonate, DHF: dengue hemorrhagic fever, DSS: dengue shock syndrome, aPTT: activated partial thromboplastin time

Source: Mallhi TH, Sarriff A, Adnan AS, Khan YH, Hamzah AA, Jummaat F, Khan AH. Dengue-induced Acute Kidney Injury (DAKI): A Neglected and Fatal Complication of Dengue Viral Infection-A Systematic Review. Journal of the College of Physicians and Surgeons Pakistan. 2015b Nov; 25(11):828-34.

Impact of Dengue Virus (DENV) on Kidney

Viral infection-induced renal injury might be due to a direct cytopathic effect of the viral protein on the glomerular and tubular cells, an in situ immune-mediated mechanism triggered by viral antigens bound to glomerular structures, tissue injury caused by immune complexes composed of viral antigens and antiviral antibodies and damage caused by inflammatory mediators released in response to the glomerular or tubular cytopathic effects of the viral antigens.

Analyses of autopsies or biopsies of human cells infected with the dengue virus using immunohistochemically and in situ hybridization techniques have detected viral antigens in the tubular epithelial cells. Jessieet al.analyzed tissue samples of rats infected with DEN-1 and did not find viral RNA in the samples, which suggests that viral replication does not occur in the renal tissue [33, 34].

Management of Dengue Induced AKI

Careful assessment of the warning signs of severe dengue and the patient's blood volume are crucial for the prevention of AKI. Fluid replacement should be performed carefully to avoid overload producing a consequent worsening of intravascular fluid extravasation, which might increase morbidity and mortality. Fluid replacement must be initially performed with crystalloid solutions, while use of colloids should be restricted to cases of unresponsive shock. The amount of infused fluid should be the minimum needed to stably maintain the hemodynamic conditions until the increased vascular permeability is reversed.

The use of parenteral corticosteroids in cases of severe dengue is controversial, and there are no recommendations for their use in patients with AKI. Serum CK levels should be monitored to allow for early diagnosis of rhabdomyolysis and the institution of adequate preventive measures. Once a diagnosis of AKI is established, support treatment should be timely and adequately performed to prevent worsening of the condition.

Renal replacement therapy is currently indicated as conventionally used, because there are no specific recommendations for the proper time to begin treatment, dosing or modality in dengue patients [33].

AKI seems to be a frequent complication of severe dengue that increases the morbidity and mortality of the affected patients. Its Etiopathogenesis is probably multifactorial, caused by intense systemic inflammation, hemodynamic instability, hemolysis, rhabdomyolysis and acute glomerulitis. Currently, there are no specific recommendations for either conservative treatment or dialysis of patients with dengue, and the effects of AKI on the quality of life, survival and kidney function of survivors are unknown. Prospective studies aimed at establishing the incidence of and risk factors for dengue-associated AKI, its Etiopathogenesis, and the best therapeutic approach for patients with dengue and **AKI** are urgently needed.

DENGUE IN CHRONIC KIDNEY DISEASE PATIENTS

In consideration of diagnosis in **DF**, the symptoms of **DF** are nonspecific. Early recognition of the warning signs of **DHF** (intense continuous abdominal pain, persistent vomiting, and restlessness or lethargy) and early treatment are of prime importance in reducing the mortality rate. For patients with **CRF**, the presentations of **DF** are not obvious, and diagnosis is more difficult. The warning signs are even similar to the presentation of uremia. In the diagnostic criteria of **DHF**, hemoconcentration, pleural or other effusions, and hypoalbuminemia are easily ignored in uremia. In such cases diagnostic delay of dengue can occur that may relate to high mortality. Even if physicians have made early and accurate diagnoses of **DF**, the treatment of **DF** in patients with **CRF** is still difficult. Because no specific antiviral treatment of dengue virus exists, the only treatment is supportive care, such as rest, adequate fluid intake, and antipyretics. [2,10] for treatment of DHF/DSS, the three most important issues are fluid supply, electrolyte balance, and bleeding control. Because of capillary leakage, the problem of fluid loss is more severe than blood loss in DHF/DSS, and the strategy of treatment must focus on the restoration of volume status and maintenance of blood pressure.10 In patients with **DSS**, if fluid is inadequate, prolonged shock will lead to refractory shock, and mortality will occurr.11 However, if too much fluid is given, acute pulmonary edema occurs. Therefore, how to monitor the fluid status and provide the optimum fluid intake is very important in patients with **DSS**. Urine output, central venous pressure catheter, and chest x-ray are all monitoring tools for evaluation of fluid status. Among these tools, urine output is a good, simple indicator. However, in **CRF**, especially in dialysis patients, the urine output cannot be an indicator for the monitoring of fluid status. If patients without **CRF** have fluid overload during the treatment period, we may use diuretics to correct fluid status, but in patients with renal failure, the diuretics may only have a limited effect, and eventually dialysis may be required. This makes it more difficult to maintain the balance on fluid supply. Therefore, we recommend more frequent evaluation of fluid status and careful monitoring of the fluid supply in patients with **CRF** complicated with dengue viral infection. In particular, a central venous pressure (**CVP**) catheter is necessary for patients with **DHF**/**DSS**.

Concerning the fluid solution for resuscitation of **DSS**, there are controversies between crystalloid or colloid solutions. The **WHO** recommends immediate volume replacement with isotonic solutions but plasma or colloid solution for profound or persistent shock.[11] One double-blind, randomized comparison of three kinds of intravenous fluids for initial resuscitation of Vietnamese children with **DSS** showed that Ringer lactate is beneficial, and it is thus indicated for children with moderately severe **DSS**. Dextran 70 and 6% hydroxyethyl starch also have similarly beneficial effects in children with severe shock.12 However, another study showed that the longest recovery times occurred in patients resuscitated with Ringer lactate in comparison with the other three kinds of fluids (normal saline, gelatin, and dextran).[11] Ringer lactate also contains potassium and lactate, and they may theoretically carry the risk of hypokalemia and worsen tissue acidosis by lactate accumulation if not metabolized normally. Therefore, this

treatment must be used with caution in patients with **CRF**. Dextran 70 has been reported as the preferred solution for acute resuscitation in **DSS**, [13] but it may induce severe anaphylaxis.[12] Starch is an effective colloid solution and is preferred in children with severe **DSS**.[12] However, the safety of starch is not well established in patients with **CRF**. Therefore, these three kinds of intravenous fluids seem unlikely to be applied to patients with **CRF**. More research is needed to find the most suitable fluid in patients with **CRF** with **DSS**. During the treatment of **DHS/DSS**, in addition to the requirement of a large amount of fluid, the acid-base and electrolyte balances are important issues. The patients with **CRF** have greater chances of developing acidosis and electrolyte imbalance, especially at a shock status. The majority of these imbalances can only be corrected by dialysis, such as hypokalemia occurring in oliguric renal failure. However, it is difficult to perform hemodialysis in patients in a shock state without further compromising the hemodynamic. In this case, continuous renal replacement therapy (**CRRT**) should be considered. Coagulopathy and severe thrombocytopenia are other important complications in **DHF** that will cause severe bleeding and mortality. Among these varieties of severe bleeding, gastrointestinal bleeding is the most common. [14] Pulmonary and brain hemorrhage are other potentially fatal complications.[15]For the treatment of gastrointestinal bleeding, blood transfusion is still the mainstay of management, and endoscopic injection therapy is not effective as adjuvant treatment. Many patients with **CRF**, in addition to coagulopathy and severe thrombocytopenia, also have platelet dysfunction in quality. This bleeding diathesis will make the situation of bleeding difficult to stop.

To improve the bleeding diathesis in uremic patients, decompressing has been suggested for temporary correction of bleeding time.[16] Decompressing (1-deamino-8-Darginine vasopressin), also called **DDAVP**, can shorten the prolonged bleeding time, release endothelial haemostatic factors, and promote the adhesion of platelets to the vascular subendothelium17; therefore, it is used to improve platelet function in von Willebrand disease and hemostasis in uremic patients. Furthermore, because decompressing also has the effect of water retention, it seems reasonable to restore body volume in **DHF/DSS**. The implications of decompressing in DHF have been reported; further studies are needed for validation of that effect [35].

For the general population, the mortality of **DHF** is 1–5%. The difficulty in diagnosis and the treatment dilemma in patients with **CRF** cause a high risk of mortality, which may be attributed to the overlap in symptoms and signs between **CRF** and **DF**. Where a high index of clinical suspicion is paramount in making a diagnosis, a travel and vector exposure history should be obtained where appropriate, especially for patients with **CRF**.

FUTURE PERSPECTIVE

Dengue Induced Nephropathies are least appreciated area that requires more larger and controlled studies in order to evaluate its pathophysiological mechanisms, short term and long term outcomes among patients who survive an episode of these nephropathies especially acute kidney injury (AKI).

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