

## Dengue Infection Causing Acute Kidney Injury

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### Abstract

**Objective:** We aim to report patients coming to this tertiary care center, developing acute kidney injury (AKI) after Dengue infection.

**Methods:** An observational study of patients identified as having AKI after Dengue infection. AKI was defined according to RIFLE criteria with sudden rise in creatinine or decline in urine output or both. All patients had normal size non obstructed kidneys on ultrasonography, with no previous co morbid. Dengue was diagnosed on detection of dengue-specific IgM capture antibody or a four-fold or greater increase of dengue-specific IgG capture antibody by ELISA.

**Results:** From January 2000 – December 2014, total 3525 patients with AKI registered at this institution, of these 43 (1.21%) developed AKI in association with dengue infection. Average age of patients was  $34.65 \pm 14.50$  (range 16-90 years) with 31 male and 12 female. Jaundice and oligo-anuria were most common associated symptoms with fever. Renal replacement therapy required in 31 (72.09%) patients. Complete recovery was seen in 37 (86%), while 6 (14%) died during acute phase of illness. Age, jaundice, thrombocytopenia and shock were the factors significantly associated with high mortality.

**Conclusion:** AKI though less reported, remains dreaded complication of dengue virus infection. With involvement of liver, circulatory system and prolonged thrombocytopenia mortality is high.

**Keywords:** AKI; RIFLE criteria; Dengue infection; Thrombocytopenia

### Introduction

Dengue is an important viral infection transmitted through mosquito bites. It is widely spread in tropics and sub-tropical countries. Reported incidence is 50-100 million new cases every year across the globe [1-5]. From Pakistan first case of dengue was reported in 1982 [6].

The clinical presentations of dengue infections range from mild flu-like illness to the severe forms of hemorrhagic fever and shock syndrome which may cause mortality [1,3]. Previously patients with dengue used to be classified under dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). In 2009 WHO has revised this classification and new classification has either dengue or severe dengue [1,5]. Dengue can affect various organs simultaneously or one at a time, involvement of liver, hematological, nervous and respiratory system has been widely reported [7]. A spectrum of renal involvement reported with dengue infection, ranges from Proteinuria, glomerulonephritis, IgA nephropathy to acute kidney injury (AKI) [8], then case reports showing rhabdomyolysis and acute tubular necrosis are there in literature [9,10]. Hemolytic uremic syndrome (HUS) also reported as associated pathology with dengue infection [11]. The prevalence of AKI from Columbia has been reported 1.6% among 617 children with hemorrhagic fever [12] and in another report from adult patients it was 3.3% [13].

Dysregulated inflammatory response to dengue viral infection leads to shock like state.

AKI is mainly associated with hemorrhagic fever and shock syndrome and may present as part of multi-organ failure. Transient disruption in the function of endothelial layer is characteristic of dengue infection, which eventually leads to multiple consequences [1].

Here we aim to report our experience of patients infected with dengue and presented to Sindh Institute of Urology and Transplantation, Karachi; with AKI.

### Patients and Methods

This study is based on observation of 43 patients with AKI after infection with dengue; from a retrospective chart review of all patients admitted to the Sind institute of Urology and Transplantation, Karachi, Pakistan between January 2000 and December 2014. AKI was identified and staged according to RIFLE criteria [14]. Dengue was diagnosed on detection of dengue-specific IgM capture antibody or a four-fold or greater increase of dengue-specific IgG capture antibody by ELISA.

Patients were labeled in state of shock when found abnormal body temperature, disproportionately increased heart rate, low blood pressure, increased respiratory rate and  $\pm$  compromised oxygen saturation.

Only patients with no past medical history were included and all patients had normal size non obstructed kidneys on ultrasonography.

Variables recorded for each patient on day of admission include age, history, duration of insult, oliguria, anuria, vitals, general and systemic examination, hemoglobin, total leukocyte count, platelet count, prothrombin time, activated partial thromboplastin time, blood peripheral film, blood urea, serum creatinine, serum sodium, serum potassium, venous bicarb, serum lactate dehydrogenase, serum bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, urine dipstick, urine microscopy, ultrasonography, parenteral fluids before renal replacement therapy, renal replacement therapy, sessions of hemodialysis and outcome. All laboratory results used for evaluation were from first day of hospitalization.

Patients divided into 3 groups of 5 year each, first from 2000-2004, only 2 cases of dengue were seen, then between 2005-2009, nine cases, and last 5 years 32 cases were brought in AKI after dengue infection.

Institutional ethical review committee was approached to seek permission for publishing the data and verbal permission was granted.

### Statistical methods

Quantitative variables reported as means ± SD and Qualitative as percentages. For univariate analysis of mortality risk factors student's t-test applied, categorical variables summarized as frequencies and percentages and then analyzed by the Chi-square test or Fisher exact test where appropriate. Statistical analysis was done on SPSS version 20.0.

### Results

Between Jan. 2000 to Dec 2014, 43 (1.21% of total AKI) patients with dengue causing AKI, registered to this hospital. Average age of patients was 34.65 ± 14.50 years (range 16-90), with 31 male and 12 female.

Jaundice and decline in urine output were common associated symptoms with fever. Vomiting was reported in 22 (51.16%). Twelve (27.9%) patients presented in state of shock and required volume expanders ± inotropes on arrival. Neurological involvement that ranges from drowsiness to frank coma was found in 4 patients, none of our studied patients had mononeuropathy. Presenting symptoms are tabulated in Table 1. Diarrhea was reported as profuse and watery in 5 (11.62%) patients. Extensive hemorrhagic/ purpuric rash was seen in 6 patients.

As far as laboratory parameters are concerned, majority of patients had anemia, thrombocytopenia, and advanced uremia, 14% had high serum potassium levels and 35% had low sodium on presentation. International normalized ratio for coagulation found deranged in 10 (23.25%) patients. Urinalysis was available from 32 patients, on dipstick proteinuria of 1-3+ found in 20 and microscopic hematuria in 28 patients (Table 2). We have serum lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) available for all patients (Table 2), but creatine phosphokinase (CK) is available for only 6 patients, it was in normal range in 3, mildly increased in 1 and moderately in 2 patients.

Symptoms / signs	No (%)
Fever	43 (100)
Jaundice	33 (76.74)
Oligo-anuria	31 (72.09)
Vomiting	22 (51.16)
Presented in state of shock	12 (27.90)
Hemorrhagic/Purpuric rash	6 (13.95)
Diarrhea	5 (11.62)
Altered level of consciousness (ALOC)	4 (9.3)

**Table 1:** Presenting symptoms in patients developing AKI after dengue infection (n=43).

Parameters	Values
Haemoglobin mean ± SD in g/dl	10.29+5.64 (range 5-16.7)
Platelet count mean ± SD	52.65+41.77 (range 10,000-180,000)
Blood Urea mean ± SD mg/l	257.44+125.77 (range 86-585)
Serum Creatinine mean ± SD mg/l	10.12+5.96 (range 3-35.2)
Serum LDH mean ± SD U/L	1131.94 ± 1168.36 (range 34-5280)
Serum AST mean ± SD U/L	425.78 ± 893.58 (range 21-4380)
Serum ALT mean ± SD U/L	208.66 ± 282.88 (range 16-1087)
Deranged INR (%)	10 (23.25)
Hyperkalemia, K>5.5 meq/l (%)	6 (13.95)
Hyponatremia, Na<130 meq/l (%)	15 (34.88)
Microscopic hematuria (%)	28 (87.5)*urinalysis available for 32patients
Proteinuria 1-3+on dipstick (%)	20 (62.5) *urinalysis available for 32 patients

**Table 2:** Laboratory findings in patients developing AKI after dengue infection (n=43).

Renal replacement therapy was required on arrival in 31 (72.09%) patients, it was hemodialysis in all. Complete recovery seen in 37 (86%), while 6 (14%) died during acute phase of illness.

Statistical tests were applied to differentiate among poor prognostic factors in terms of mortality. Age, jaundice, thrombocytopenia and shock were the factors associated with high mortality with p value of <0.05 (Table 3).

Parameters	Recovered (n=37)	Died (n=6)	P value
Age mean ± SD in years	32.57 ± 14.18 (16-90)	47.5 ± 9.35 (30-35)	0.008

Sex M/F	26/11	5/1	0.455
Days of insult mean ± SD	10.65 ± 5.87 (3-28)	9 ± 4 (4-14)	0.514
Excessive vomiting	19	3	1
Oligo-anuria	27	4	0.799
ALOC	3	1	0.465
Jaundice	28	5	0.022
Bleeding diathesis	9	2	0.637
Platelet mean ± SD	77 ± 88.81 (10-421)	32.33 ± 23.55 (13-79)	0.016
Deranged coagulation	8	2	0.122
Urea mean ± SD	250.81 ± 127.16 (86-585)	292.33 ± 133.15 (148-459)	0.501
Creatinine mean ± SD	9.66 ± 5.86 (3-35.20)	11.56 ± 6.41 (4.78-22.39)	0.521
Sodium (meq/l) mean ± SD	132.05 ± 6.31 (116-144)	138 ± 13.65 (123-159)	0.339
Potassium (meq/l) mean ± SD	4.2 ± 0.95 (2.4-6.4)	4.5 ± 1.59 (2.9-7.4)	0.72
Serum bilirubin mean ± SD	5.52 ± 9.44 (0.34-46.31)	5.41 ± 8.64 (0.96-20.80)	0.981
Sgot mean ± SD	462.03 ± 946.15 (21-4380)	157.6 ± 160 (31-393)	0.083
Sgpt mean ± SD	214.59 ± 296.69 (16-1087)	164.8 ± 158.85 (21-349)	0.578
Ldh mean ± SD	1063.26 ± 1093.55 (34-5280)	1841.67 ± 1938.39 (378-4040)	0.56
Proteinuria 1-3+on dipstick	18	2	
Microscopic hematuria	24	4	0.665
Presented in shock (no. of patients)	7	5	0.004
Sessions of HD mean ± SD	3.08 ± 1.67 (1-7)	1.8 ± 0.83 (1-3)	0.109

**Table 3:** Comparison of different parameters and their significance in Patients developing AKI after Dengue infection.

## Discussion

Dengue is a vector born viral infection, transmitted to human beings via mosquito bite. The infection may remain subclinical or asymptomatic in some, mild illness to other while life hazard to still few. Multi system involvement including hepatic, circulatory, nervous system, coagulation and renal has been reported in literature [15,16]. Involvement of nervous system ranges from mononeuropathy, polyneuropathy, encephalitis and Guillain-Barre syndrome [9,17]. In present study we have not found mono or poly neuropathy in any of our patients but 4 patients arrived in altered state of consciousness, it was drowsiness and confusional state in 2 while Glasgow coma scale of 5 in couple of patients. Among these 4 patients 3 had low sodium on day of hospitalization which was 128-129 meq/l and one had sodium in normal range. Overall in study population 35% had hyponatremia (sodium of <130), a case controlled study published from Thailand also reports significant hyponatremia in children with dengue infection in comparison to children with other febrile illness [18]. With present study we have shortfall of not having urinary sodium available for all patients with hyponatremia and thus cannot comment on renal handling of sodium in dengue infection. A study published from our country, the same city, has reported central nervous system involvement in 2.1%, which is lower than what we found in our

patients but then reason is that we only see patients who already had developed renal failure while Khalil et al. have reported all dengue patients in an internal medicine environment [7]. Acute diarrhea has also been reported in association with dengue infection in previous studies [17], we have also found it a feature in 5 patients of present study.

Rhabdomyolysis and myositis has been reported by Acharya et al. [9], we have LDH and AST available for all and CK for limited number of our studied population and in light of our past experience we can comment that rhabdomyolysis was not a feature in present study [19,20].

Barsoum et al. have reported Proteinuria and abnormal urine sediment with dengue infection [21] but rare manifestations as IgA nephropathy, HUS and lupus in addition to AKI are also known on spectrum of renal involvement with dengue [8,11]. With established AKI there are invariably signs of capillary leakage, decline in blood pressure and multi organ involvement/ failure [8,22].

AKI in absence of hypotension, rhabdomyolysis or use of any nephrotoxic agent has also been reported in past indicating towards direct renal injury with dengue infection [23], this possibility exists in

few of our patients. Renal biopsy was not performed to confirm the verdict, so this remains a limitation to the study.

In our experience patients who were brought in state of shock, comparatively older age, jaundice on presentation or with more prolonged thrombocytopenia shown poor prognosis. Others have reported presence of AKI as independent mortality risk factor with dengue infection [7]. Whereas shock syndrome also reported poor prognostic factor in literature [24].

Recently published is the use of vaccination against dengue and remarkable decline in number of hospital admission due to dengue infection [25], so the complications related to dengue can be reduced in future.

## Conclusion

There are many faces of renal involvement with dengue infection; even AKI may results from various mechanisms. Early detection of renal involvement and timely steps towards management may reduce morbidity and mortality. Recent development with vaccination against virus seems promising.

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