

## ORIGINAL ARTICLE

# Recurrent Acute Kidney Injury in Tropics-Epidemiology and Outcomes

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## Abstract

**Background-** Acute kidney injury (AKI) is now an established and preventable cause for chronic Kidney disease. Poor outcome of Acute Kidney Injury is influenced by severity and duration of AKI.

We hypothesize that recurrent episodes of acute kidney injury are associated with adverse renal and patient related outcome.

**Methods-** Study was undertaken to look into etiological risk factors for recurrent AKI and its effect on renal and patient related outcome. This retrospective analytical study was conducted at tertiary care health care centre from northern part of India from January 2003 to December 2013. All patients with the diagnosis of "acute renal failure" or "acute kidney injury" as their hospital admission diagnosis was identified and individuals with recurrent Acute Injury were included in the study.

**Results-** Recurrent acute kidney injury was found in 21 (0.56%) of 3698 patients who presented with acute kidney injury during the 10 years period. Topical infections were the most common etiology of recurrent AKI followed by rhabdomyolysis and intravascular hemolysis leading to pigment nephropathy. Acute tubular necrosis was the most common histopathological diagnosis among patients biopsied. As the episodes of AKI increased from 2 to >2 episodes, there was poor immediate as well as late renal outcome. 50% were proteinuric and 87.5% were hypertensive at 1 year among patients who had >2 episodes of AKI while it was 15.3% and 7.69% among patients having < 2 episodes respectively.

**Conclusion-** Recurrent episodes of AKI are associated with poor patient and renal outcome suggesting that each episode of acute kidney injury needs close evaluation and follow up following hospital discharge with particular attention to renal outcomes.

## Introduction

Acute kidney injury (AKI) is now a well established and preventable risk factor and a cause for development of chronic kidney disease (CKD), end stage renal disease (ESRD) and mortality.<sup>1-5</sup> This is due to reductions in renal mass and nephron number, vascular insufficiency, cell cycle disruption, and maladaptive repair mechanisms which appear to be important modulators of progression to CKD.<sup>13-16</sup> The poor outcome of AKI is affected by severity, duration and frequency of AKI.<sup>8-12</sup> The effect of severity and duration of AKI is well studied in comparison of frequency of AKI. Recurrent episodes of AKI might

be associated with development of CKD and poor patient related outcome, although not studied systematically (10). However USRDS data mentions occurrences of recurrent AKI to be almost 30% of which 0.3% developing ESRD especially among that needing dialysis.<sup>17</sup>

We hypothesize that recurrent episodes, acute kidney injury are associated with adverse renal and patient related outcome as observed with severe and prolonged duration of AKI. Hence we undertook to study

etiological risk factors of recurrent AKI and its effect on renal and patient related outcome.

## Aims and Objective

1. To look for incidence and etiology of recurrent acute kidney injury in our population.
2. To study the effect of recurrent AKI on patient and renal related outcomes.

## Material and Methods

This retrospective analytical study was conducted at tertiary care health care centre from northern part of India from January 2003 to December 2013.

Patient data were retrieved from the computerized hospital based electronic information system and patient record files. All records of the patient's history, physical examination, laboratory investigations and discharge reports, their clinical presentation, etiological diagnosis and outcomes were evaluated and examined by two nephrologists. A clinical and histopathological diagnosis was made after scrutinizing all the details. All patients with the diagnosis of "acute renal failure" or "acute kidney injury" as their hospital admission diagnosis was identified and individuals with recurrent Acute Injury were included in the study.

All patients having recurrent acute kidney injury with commodities like Chronic liver disease, Hepatorenal syndrome, and decompensated heart failure were excluded.

The definition of Acute kidney injury (as defined by rifles criteria) was a threefold increase in serum creatinine or decrease in GFR of > 75% or urine output of <3ML/Kg per hour for >24

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**Table 1: Demographic profile of recurrent acute kidney injury N=21**

Variables	Results
Age (mean)	26.7 ± 12.3 years
Gender (M/F)	12/9
Mean duration of hospital stay	44.8 ± 29.3 days
No. of past Episodes of AKI (mean)	2.5 ± .65
Dialysis dependency at presentation (number)	16
Mean serum creatinine at presentation	5.8 ± 4.1
Mortality (number)	2
Mean follow up of patients	11.2 ± 8.2 months

hours, also an acute rise of 0.5 ml/dl of serum creatinine was included.

Definition of recurrent AKI-An episode of acute kidney injury as described by the above definition with a history of similar episodes in the past, irrespective of etiology. Patients with diabetes, hypertension, CKD were excluded from this study. These patients had documented recovery of renal function following the earlier episode.

The first serum creatinine obtained after admission to the hospital was taken as baseline value. Oliguria was defined as urine output <400 mL/24 h.

Acute tubular necrosis was considered when renal functions did not improve after correction of possible pre-renal causes and when hepato-renal syndrome and vascular, interstitial, glomerular and obstructive etiologies were ruled out. All patients with evidence of CKD at time of recurrent AKI were also excluded. This was done to avoid biasness in analysis...

Acute glomerulonephritis was considered on a case with histological confirmation except for acute post-infectious state with clinical and biochemical markers substantiating the diagnosis.

Acute tubulointerstitial nephritis was considered in the state of high grade of clinical suspicion or a histological demonstration.

The indication for kidney biopsy considered in which the etiology of recurrent AKI needed to be obtained, hypertension, active urinary sediments non recovery of renal function were other indications for biopsy.

Patients were evaluated on the following outcomes:

Immediate outcome means renal and patient related outcome at 30 days

**Table 2: Clinical presentaion of patients with recurrent AKI**

Causes/No. of patients	Total no. of episodes	Patients with ≥2 episodes	Clinical presentation (Histological Diagnosis)	Dialysis need
Tropical infections-5	11	2		
MAKI-4	8	2	Fever, anemia, jaundice, oligouria(ATN-1,TMA-1)	2
DHF-1	2	0	Fever, anemia, thrombocytopenia, jaundice, oligouria	1
Drug induced AIN-3	7	1		
NSAIDS-1	3	1	Rash, non oliguric AKI(AIN-1)	2
PPI-1	2	0	Rash, non oliguric AKI	1
Rifampacin-1	2	0	Rash, non oliguric AKI	0
IVH with ATN-4	10	1		
HS-1	2	0	Anemia, jaundice, oligouria	1
G-6-PD-2	6	1	Fever, anemia, jaundice, oligouria(ACN-1)	2
PNH-1	2	0	Fever, anemia, leucopenia, jaundice, oligouria	1
TMA-3	7	2		
D+ve HUS-1	2	0	Fever, oligo-auria, TMHA	1
CFH Ab-1	2	1	Fever, oligo-auria, TMHA( HUS-1)	1
ADAMTS def.-1	3	1	Fever, oligo-auria, TMHA(HUS-1)	1
Rhabdomyolysis-3	8	1		
Seizure disorder-1	3	1	Recurrent seizures, muscle soreness, oliguria, high CPK-MM	1
Alcoholism-1	3	0	Alcohol binges, muscle soreness, oliguria, high CPK-MM	1
Mcardles disease-1	2	0	Strenuous exercise, fever, muscle soreness, oliguria, high CPK-MM	1
IgA NP with ATN-3	7	1	Cola colour urine and oliguria after sore throat(ATN-3)	2

MAKI-Malarial acute kidney injury, DHF-Dengue hemorrhagic fever, AIN-Acute interstitial nephritis, PPI-proton pump inhibitors, IVH-Intravascular Hemolysis, ATN-acute tubular necrosis, HS-hereditary spherocytosis, PNH-paroxysmal nocturnal hemoglobinuria, TMA-thromboticmicroangiopathy, IgA NP-IgA nephropathy, CFH ab-Compliment factor h deficiency, ADAMTS Def-ADAMTS deficiency, G6PD -G6PD enzyme defecien

of the illness categorized as complete recovery of renal function, partial recovery of renal function not requiring renal replacement therapy (RRT), Non recovery of renal function, discharged on RRT, eGFR at 3 months or in-hospital mortality.

Late outcome means renal and patient related outcome at 6 months and 1 year of the illness was defined as as complete recovery, partial recovery not requiring renal replacement therapy (RRT) or eGFR <50%, dialysis dependency, eGFR at 1 year, presence of hypertension, urinary abnormalities and mortality.

#### Statistical Analysis

Values were expressed as mean ± standard deviation. Univariate analysis to identify risk factors was performed using chi-square test or Fisher's exact test for discrete variables and Student's "t" test for continuous variables. Thirty-six variables, including age, need for Intensive Care Unit care, and hypotension at admission, jaundice, oliguria, Icterus and encephalopathy were compared in survivors and

non-survivors. Statistical analysis was done with SPSS 15 software for windows. A P-value less than 0.05 were considered significant.

#### Results

A total of 3698 patients presented with acute kidney injury during this 10 years period (16.3%) of all patients seen during this period. Recurrent acute kidney injury was found in 21 (.56%) patients. The demographic profile is mentioned in Table 1.

Causes of Recurrent Acute Kidney Injury (Table 2).

The Most common cause for Recurrent AKI in our study was Tropical infections followed by rhabdomyolysis, drugs and intravascular hemolysis leading to pigment nephropathy. Among the tropical infections MAKI (Malaria Acute kidney injury) presented as the most common etiology followed by dengue. Prolonged disease duration, oligonuric status and DIC were poor prognostic markers for renal outcome in this subgroup.

**Table 3: Renal outcome among recurrent AKI**

Immediate Renal outcomes	
Immediate outcomes (renal / patient outcome)	Number (21)
Mortality	1 (4.7%)
Partial renal recovery (serum creatinine >1.5 mg% at 30 days of Acute kidney injury)	9 (42.8%)
Complete recovery (Serum creatinine < 1.5 mg% at 30 days of acute kidney injury)	8 (38.09%)
Dialysis dependency	3 (5.4%)

The most common causes of Rhabdomyolysis leading to AKI was diagnosed in a setting of an unconscious patient with repeated episodes of seizures with muddy urine, history of recurrent acute kidney injury following heavy bout of alcohol and acute kidney injury following intense exercise, who was later diagnosed as Mardles disease in each on respectively. All had evidences of myoglobinuria along with raised CPK levels.

Intravascular Hemolysis is an important cause for recurrent acute kidney injury in our study population picked up in a setting of AKI with evidence of jaundice and hemolytic anemia. Among the prominent causes for AKI were drug induced, Enzyme defect and Paroxysmal nocturnal hemoglobinuria.

Thrombotic microangiopathy was a concern for recurrent AKI in 3 with clinical and laboratory evidences suggestive of the diagnosis.

Among the other important causes of recurrent AKI was IgA nephropathy presenting as hematuria leading to ATN and renal failure among 3 patients biopsy proven in 1.

Histological diagnosis of all the 21 patients was analyzed. 8 patients underwent renal biopsy during the hospital stay. The most common indication for renal biopsy in our population was persistent renal failure of more than three weeks duration. Absence of an obvious cause for recurrent AKI and extra renal manifestation suggestion of a systemic disease were the other common indications of renal biopsy. In those patients who did not undergo renal biopsy, a "probable" histological diagnosis was assigned based on patient's history, clinical findings, laboratory investigations and hospital course

When histological diagnosis was

**Table 4: Renal outcome in relation to episodes of recurrent acute kidney injury after 3 months of discharge**

Outcome	2 episodes (N=13)	>2 episodes (N=8)
Mortality	1	1
Complete recovery	6	2
Partial renal recovery	5	3
Dialysis dependency	1	3
Asymptomatic urinary abnormality	2	4
Development of hypertension	1	7

analyzed, acute tubular necrosis was the most frequent cause of whom pigment nephropathy secondary to hemolysis was the most important cause. Drug induced Acute interstitial nephritis was an important cause of concern especially use of drugs like NSAIDs and proton pump inhibitors.

Thrombotic microangiopathies was the histological diagnosis among 3 patients, 1 had history of malarial fever and evidences of hemolysis with non resolving AKI with clinical diagnosis of HUS (secondary to malaria), while the other 2 had deficiency of ADAMTS 13 and CFH antibody in each.

#### Episodes of Acute Kidney Injury

In relation to episodes of Acute kidney injury, 13 patients had 2 episodes (26 episodes) while 8 patients had >2 episodes (24 episodes). Those patients who had >2 episodes of AKI (number=8), 4 of them underwent biopsy of which 1 had IgA nephropathy with ATN, while the others<sup>2</sup> had thrombotic microangiopathy and Acute interstitial nephritis<sup>1</sup> due to NSAIDs.

Mean duration of episodes of Acute kidney injury between various groups was not found to be significant factor in terms of non recovery or need for dialysis

#### Patient Outcome

Overall mortality among patients with recurrent Acute kidney injury was 9.5% (2 patients). 1 patient who was dialysis dependant succumbed during the hospital stay while another 1 died after an average of 4.5 months from the last episode of AKI.

#### Renal outcome (Table 3)

Out of 21 patients with recurrent AKI, the immediate outcomes (within 30 days) in terms renal recovery showed that 9 patients had partial recovery of renal functions while 3 were discharged on long term RRT 38.09 % of them showed complete recovery of their

renal function. Late outcomes observed at 1 year follow up showed that 23.8% were dialysis dependant, 42.1% were hypertensive while 26.3% showed abnormal urinary sediments.

In relation to episodes of AKI (Table 4), as the episodes of AKI increased from 2 to >2 episodes, there was poor immediate as well as late renal outcome. 50% of who were protienuric and 87.5% were hypertensive at 1 year was observed patients with >2 episodes while it was. 15.3% and 7.69% among patients having <2 episodes respectively.

#### Discussion

This study is perhaps first of its kind to look into incidence, etiology and outcomes of recurrent AKI. We observed that tropical infections were the most common etiology of recurrent AKI and ATN was the most common histopathological diagnosis. Poor patient and renal outcome was observed in patients who had more than 2 episodes of AKI.

The incidence of Recurrent AKI in our study population was 0.56% patients among all patients with acute kidney injury. USRDS data mentions occurrences of recurrent AKI to be almost 30% of which 0.3% developing ESRD especially among that needing dialysis.<sup>17</sup> This lower incidence in our study population could be attributed to the stringent inclusion criteria excluding patients associated with comorbidities like DM, cardiac and liver disease.

Tropical Infections were the most common cause of recurrent AKI followed by rhabdomyolysis and intravascular hemolysis in our study population. There is paucity of data on etiology of recurrent AKI. However tropical infections are the most common cause of community acquired AKI in tropics.<sup>24</sup> In tropics, the hot and humid climate which is conducive for persistence of micro-organisms, their reservoirs and vectors along with the great biodiversity adds to complex interactions between them translating into increased susceptibility to infection which is further complicated by poor access to health care services, leading to AKI.<sup>25</sup>

Despite the variable etiology for Recurrent AKI, ATN was the most common histopathological diagnosis.

Unlike developed countries, in developing countries, ATN due to community acquired infection remains the common cause in tropics.<sup>21,22</sup> Published data from our own centre on CAAKI revealed ATN as second most important histology following AIN.<sup>23</sup> The probable difference could be due to easy availability of over the counter medications and frequent use of drugs from alternate system of medicine besides higher index of early suspicion while biopsying these patients.

The immediate and late outcome was inferior in patients with increase in number of episodes of AKI ( $\geq 2$ ). Evidences suggest that an episode of acute kidney injury is associated with an increased risk of dying that persists after discharge from the hospital.<sup>27-30</sup> Hence patients with AKI had a 13-fold increased risk of CKD that progressed to kidney failure compared to those without AKI. Thakar et al<sup>31</sup> observed that individuals experiencing two or more episodes of AKI were much more likely to progress to stage 4 CKD than patients who experienced only one episode of AKI. These data are consistent with the hypothesis that for some patients a single episode of AKI has biologic ramifications beyond the acute event, engendering an ongoing state that predisposes to the development of further injury, manifested differentially in time as worsened AKI (short-term) or the development or worsening of CKD over longer periods. Some patients can fully recover from their initial AKI, but subsets of AKI survivors appear to go on to experience vicious cycles of intertwined AKI and CKD. It is likely that the severity of renal injury along with other clinical, treatment, and host risk factors mediate such processes.

## Conclusion

Each episode of acute kidney injury needs close evaluation for etiology and follow up following hospital discharge as it is associated with poor patient and renal outcomes. Tropical infections are the most common cause of recurrent AKI, which are preventable.

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