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To Study the Clinical & Aetiological Spectrum of Acute Febrile Illness with Acute Kidney Injury in Admitted Patients

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Abstract

Background: Infectious diseases are an important causes of acute kidney injury. Dengue, malaria, scrub typhus, acute gastroenteritis and pneumonia are some of common infectious diseases associated with kidney injury. Malaria was the commonest reported cause in various studies.

Aim and objectives: To study the clinical and etiological spectrum of acute febrile illness with acute kidney injury in admitted patients and to find the correlation between etiological diagnosis of fever and acute kidney injury.

Material and methods: A prospective observational non-randomised study conducted in Department of General Medicine of Dr. Sushila Tiwari Government College & hospital, Haldwani. The study population was drawn from patients who presented with acute febrile illness with acute kidney injury.

Results: Total 130 eligible patients were taken, 81 males and 49 females with mean age 47.5±17.5 years. The most common symptom and sign was nausea/vomiting and shock 41(31.5%) and 98(75.4%) respectively. Most common etiology was sepsis/MODS 95(73.1%) and pre-renal failure was the most common type of renal failure.

Conclusion: Knowledge of pre-existing disease in a particular geographical condition enables the clinician to start early treatment which favours a better outcome. Early and meticulous treatment of restoration of circulatory volume and early initiation of specific treatment was the reason that all the patients of present study were managed successfully by conservative treatment.

Keywords: acute kidney injury, acute febrile illness, MODS, acute gastroenteritis

Introduction

Acute Febrile Illness (AFI) is defined as all acute febrile syndromes with oral temperature over 37.5°C within the last 24 hours and duration less than two weeks. They have no specific symptoms that include all the symptoms that will not help us to localize to a particular system[1-7]. AFI with Acute Kidney Injury (AKI) is a major cause of mortality [4,6]. Malaria was

commonest reported cause in various studies. This situation demands a better syndromic approach, early treatment and prevention of complications. Delay in diagnosis and treatment results high mortality[7].

Worldwide incidence of acute kidney injury (AKI) is variable, and even more among developing countries [10-12]. Tropical acute febrile illnesses such as malaria, typhoid, leptospirosis, dengue and others are a major cause of AKI in the tropics [13,14]. There is renewal of interest with the emergence of such diseases in the developed nations and non-tropical regions due to global warming and international travelling to tropics [9, 15-18].

In India, Acute Kidney Injury constitutes 1.5% of all general hospital admissions, of which 60% are due to medical causes. The most common infective causes of AKI are: acute diarrheal diseases, sepsis, infection (malaria, dengue, scrub typhus, leptospirosis, urosepsis, pneumonia, viral illnesses).[19]

So many studies from various parts of the country shows variable spectrum of etiology and its clinical presentation. No study till date had been from Kumaun region which included the hilly, tarai and plain belt.

The present study highlighted the renal involvement in acute febrile conditions. This will go along way in improving our diagnostic ability and early management of such cases.

Aim And Objectives

Aim : To study the clinical and aetiological spectrum of acute febrile illness with acute kidney injury in admitted patients.

Objectives

- To find the correlation between aetiological diagnosis of fever and acute kidney injury.
- To evaluate the prognostic factors of acute kidney injury in relation to their aetiological diagnosis and clinical presentation.

Material and Method

This prospective observational study was carried out in the Department of Medicine at Dr. Shusila Tiwari Government Medical College and Hospital, Haldwani.

Study type & area : A prospective observational non-randomised study.

Sample size: 130 patients

Study Population: Patients admitted in the Department of General Medicine of acute febrile illness with acute kidney injury.

Study Duration: From September 2017 to August 2019**.**

Subjects and Selection Method: The study population was drawn from patients who presented with acute febrile illness with acute kidney injury. One hundred thirty consecutive patients who were diagnosed with acute febrile illness with acute kidney injury were included.

Inclusion Criteria: All admitted patients with history of fever of < 3 weeks of duration with clinical and biochemical evidence of acute kidney injury.

Patients of acute febrile illness were defined as those having morning temperature of more than 37.2ºC (98.9º F) and evening temperature of more than 37.7 ºC (99.9º F) of less than three weeks duration.

Exclusion Criteria

1. Past history of renal disease, chronic kidney disease (CKD) or proteinuria.
2. Past history of chronic disease, Diabetes mellitus, Systemic lupus erythmetosus (SLE), Rheumatoid arthritis (RA), renal stones.
3. Exposure to nephrotoxins (aminoglycosides, NSAIDS, contrast, insect bites etc.)

4. Obstetric patients and surgical patients.

Investigations

Haemoglobin was measured by acid haematin method using Sahli's haemoglobinometer.

Total leucocyte count (TLC) was measured by THOMA-ZEIS haemocytometer with improved Neubauer counting chamber.

Differential leucocyte count (DLC) was done by studying peripheral blood smear stained with Leishman stain.

Platelets counting was done by crude method, direct visualization and five part cell haematology analyzer.

Serum creatinine was done by modified Jaffe's reaction initial rate assay.

Blood urea was done by GIDH kinetic method.

Blood glucose was measured by GOD-POD method, end point assay and kinetic assay.

Bilirubin was measured by MODIFIED JENDRASSIC and GROF method.

SGOT and SGPT was done by ASAT kit Mod IFCC method.

Alkaline phosphatase was done by DEAKIT, pNPP kinetic method.

Albumin was done by bromocresol green end point assay.

Dengue ELISA and card test for IgM/IgG antibody and NS1 antigen was used based on immunochromatographic method. Dengue Day 1, J Mitra and Co. Pvt. Ltd card test was used.

Widal test was performed by using standarised TO and TH antigen (span kit name) according to the standard as described in packaged insert. Doubling dilution of 1:20 to 1:60 for initial screening followed by further dilution to achieve end titre.

Malaria card test was done by detecting malarial antigen Advantage Mal Card test, J Mitra and Co. Pvt. Ltd.

IgM ELISA scrub typhus was done for detecting IgM antibodies to Orentia tsutsugamushi by using 56kd recombinant antigen kit of InBioss India.

Peripheral blood smear done to look for abnormalities in blood cells and are routinely employed to look for blood parasites, such as those of malaria and filariasis.

The following Investigations were done only where indicated :

Sputum for AFB and Mycobacterial Culture and Sensitivity

a. In a patient with any combination of symptoms of fever, cough with sputum, weight loss, excessive night sweating for at least 2 weeks.

b. With or without features suggestive of pulmonary tuberculosis on Chest x ray.

Urinalysis History of any of the following: reduced urine output, frothy urine, hematuria; lower limb, facial, or generalized body swelling and inflammatory lower urinary tract symptoms (LUTS).

Urine culture : Patients with history of lower urinary tract symptoms like pain and discomfort in the lower back and abdominal area , pain when urinating , fever, feeling of urge to urinate frequently undergo this test.

Blood culture : This test was done in all cases of fever where diagnosis was not established after baseline tests. This was done specifically in suspected cases of enteric fever.

NCCT head : was done in patients with history of altered sensorium , headache, nausea and vomiting, abnormal body movements, history of seizure disorder.

CSF Examination was done in cases with sign and symptoms suggestive of central nervous system infection. CSF was subjected to biochemical

assessment of sugar, protein and cytological assessment by count and differential counts.

Procedure

1. Details of history, general physical examination and laboratory investigation reports were noted down from time to time using a set proforma specially designed for the study.
2. Once the specific diagnosis was reached, patients were treated for it symptomatically and specifically.
3. Once renal failure was found they were classified into 3 groups:

1) Mild 2) Moderate 3) Severe

The criteria for this classification was following:

Mild : serum creatinine 1.5-2.0mg/dl and urine output <30ml/h for 6 h

Moderate : serum creatinine 2-3mg/dl and urine output <30ml/h for 12 h

Severe : serum creatinine >3mg/dl and urine output <18ml/h for 24h or complete anuria for 12 h.

4. Special emphasis was given for the management of fluid, electrolytes, acidosis and renal output. Appropriate use of vasopressor was done in selected cases.
5. All the patients were intervened as early as possible for the etiological and supportive treatment.
6. Special attention was paid to search the presence of eschar.

Results and Observations

This study was conducted in Department of Medicine, Dr. Susheela Tiwari Hospital, Haldwani from September 2017 to August 2019. All patients with history of fever of duration 3 weeks, who fulfilling the inclusion criteria and have AKI were enrolled. Total 130 patients were included in the present study. Following results were obtained :

Table No. 1: Gender wise distribution of Patients

Gender	Frequency(n=130)	Percentage (%)
Males	81	62.3%
Females	49	37.7%

In present study, 81 (62.3%) were male and 49 (37.7%) were females (Table No.1)

Table No. 2: Age wise distribution (years) of patients

Age (Years)	Frequency (n=130)	Percentage (%)
< 21	7	5.4%
21 – 30	22	16.9%
31 – 40	19	14.6%
41 – 50	25	19.2%
51 – 60	27	20.8%
61 – 70	20	15.4%
> 70	10	7.7%

Maximum number of patients 27 (20.8%) were of age group of 51 – 60 years which was followed by age group of 41 – 50 years 25 (19.2%). Minimum number of patients 7 (5.4%) were age group of < 21 years. The Mean ± SD age of the patients in our study was 47.5±17.5 years. Patients were almost uniformly distributed in each age group of 20 to 50 years (Table No. 2).

Table No. 3: Symptoms

	Frequency (n=130)	Percentage (%)
Nausea/Vomiting	41	31.5%
Body Ache	28	21.5%
Rashes	26	20.0%
Dyspnea	23	17.7%
Jaundice	17	13.1%
Diarrhea	15	11.5%
LUTS	14	10.8%
Alt Sens	12	9.2%
Convulsions	5	3.8%

Most common symptom was nausea and vomiting 41 (31.5%) patients that was followed by body ache, rashes and dyspnea 28 (21.5%), 26 (20.0%) and 23 (17.7%) respectively. Jaundice, diarrhea and lower urinary tract symptoms (LUTS) were having similar frequencies 17 (13.1%), 15 (11.5%) and 14 (10.8%) respectively. Minimum number of patients were having altered sensorium 12 (9.2%) and convulsions 5 (3.8%) (Table No.3)

Table No. 4: Signs

	Frequency (n=130)	Percentage (%)
Shock	98	75.4%
Oliguria	40	30.8%
Hepatomegaly	36	27.7%
Anaemia	35	26.9%
Splenomegaly	33	25.4%
Chest Crackles/Rhonchi/Effusion	24	18.5%
Lymphadenopathy	22	16.9%
Edema	13	10.0%
Eschar	10	7.7%
Impaired Consciousness	8	6.2%
Neck Rigidity	3	2.3%

Most common sign was shock 98 (75.4%) followed by oliguria 40 (30.8%). Hepatomegaly and splenomegaly was seen in 36 (27.7%) and 33 (25.4%) patients respectively. Anaemia and lymphadenopathy found in 35 (26.9%) and 22 (16.9%) cases respectively. Twenty four (18.5%) patients were having respiratory symptoms in the form of crackles, rhonchi and features of effusion. Edema was seen in 13 (10%) patients. Eschar was found in 10 (7.7%) cases. Impaired consciousness and neck rigidity found in 8 (6.2%) and 3 (2.3%) cases respectively. (Table No. 4)

Etiologies : Most common etiology in acute renal failure patients was sepsis and MODS. Most common disease was malaria. Their number was 38 (29.2%). Dengue was seen in 22 (16.9%) cases. Pneumonia, acute gastroenteritis and enteric fever contributed 20 (15.4%), 15(11.5%) and 6(4.6%) patients respectively. Thirteen (10%) patients remained undiagnosed and they were classified as undiagnosed. (Figure No. 5).

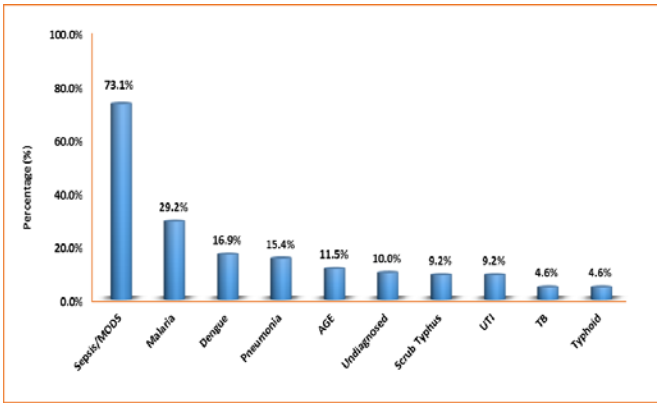

Figure 1: Etiologies

Classification of Acute renal failure: Pre-renal failure was observed in 98 (75.4%) cases and renal failure (intrinsic) was observed in 32 (24.6%) patients. All these pre-renal patients were having shock and their azotemia improved rapidly after correction of renal perfusion. (Figure No. 6).

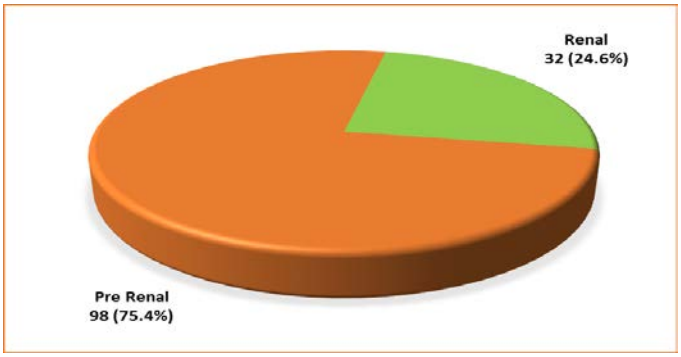

Figure 2: Classification of Acute Renal failure

Classification of renal failure and etiologies: Malaria 30 (30.6%) contributed maximum number of patients in pre-renal failure. This was followed by sepsis and dengue 29 (29.6%) and 18 (18.4%) respectively. All the

patients with infective acute gastroenteritis 15 (15.3%) were having shock and they were classified as having pre-renal azotemia. Tuberculosis 6 (6.1%) cases also contributed in pre-renal failure.

All the patients of scrub typhus, pneumonia, enteric fever, MODS and undiagnosed cases had no clinical evidence of hypoperfusion of the kidney. They all were having intrinsic renal failure. (Graph No. 7)

P value was statistically significant in present study.

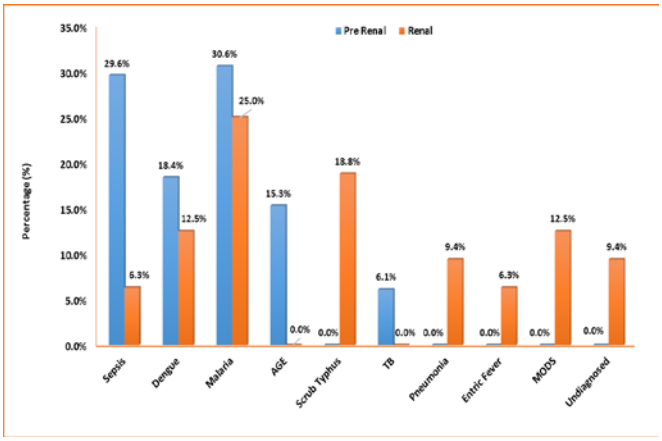

Figure 3: Classification of Renal Failure and Etiologies

Severity of renal failure in different etiologies :

The patients were classified into 3 groups on the basis of serum creatinine and urine output.

1) Mild 2) Moderate 3) Severe

Mild : Serum creatinine 1.5-2.0mg/dl and urine output <30ml/h for 6h

Moderate : Serum creatinine 2-3mg/dl and urine output <30ml/h for 12h

Severe : Serum creatinine >3mg/dl and urine output <18ml/h for 24h or complete anuria

Maximum number of patients of malaria and scrub typhus were having severe renal failure 20 (15.4%) and 12 (9.2%) respectively.

Ten (7.8%) cases of pneumonia was seen in moderate and severe renal failure each. Dengue, urosepsis, tuberculosis, acute gastroenteritis, enteric fever and undiagnosed cases 22 (16.9%), 12 (9.2%), 4 (3.07%), 9 (6.9%), 6 (4.6%) and 8 (6.2%) respectively were in the group of mild renal failure.

Twelve (9.2%), 10 (7.8%), 2 (1.5%), 6 (4.6%) and 5 (3.8%) cases of malaria, pneumonia, tuberculosis, acute gastroenteritis and undiagnosed cases respectively were having moderate renal failure. (Graph No. 9)

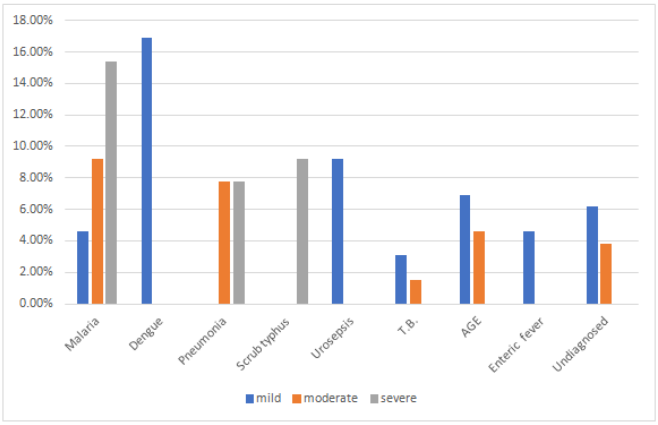

Figure 4: Severity of renal failure in different etiologies

Discussion

AKI is characterized as a rapid reduction in kidney function, resulting in failure to maintain fluid, electrolytes and base balance. Acute febrile illnesses are a common cause of AKI in developing countries.

Gender : In our study, 81 (62.3%) were male and 49 (37.7%) were females. The number of males were almost double of females. In a study done by Pratish Jacob et al (2011), M Eswarappa et al (2014) and P. S. Priyamvada et al (2018) the percentage of males were 66.9%, 63.7% and 73.3% respectively.[20-22]

Age: The maximum number of patients 27 (20.8%) were in the age group of 51-60 years followed by 25 (19.2%) in the age group of 41-50 years. The mean age was 47.5 years. In a study done by Pratish Jacob George et al (2011),[20] M Eswarappa et al (2014)[21] and Priyamvada et al (2018)[22] the common age was 30-40 years, 61-70 years and 30-70 years respectively. In all these studies there was a large variation in the age distribution. Anatomical and physiological changes that

occur in the kidney with advancing age might be the reason for increased incidence of AKI among elderly patients.

Symptoms : In the present study, all patients suffered from fever as this was the inclusion criteria. The most common symptom was nausea and vomiting 41 (31.5%), followed by bodyache 28 (21.5%). Bodyache, rashes and dyspnea were almost similar in numbers 28(21.5%), 26(20.0%), and 23(17.7%) respectively. The minimum number of patients were having convulsions 5 (3,8%). Vomiting was predominant symptom in study by K Mehta et al (2018).[23] He had 84.3% cases of patients of vomiting. Jaundice, diarrhea, and LUTS (lower urinary tract symptoms) were seen in 17 (13.1%), 15 (11.5%) and 14 (10.8%) respectively.

Signs : The most frequent sign in our study was shock 98 (75.4%) followed by oliguria 40 (30.8%). Apart from oliguria the other common physical signs were palpable liver, spleen and pallor. Their percentage was 36 (27.7%), 33 (25.4%) and 35 (26.9%) respectively. All patients who had diarrhea were having shock. Surprisingly despite of 40 (30.8%) of oliguric patients only 13 (10.0%) had edema. Maria Plataki et al (2011)[24] studied 61% of patients were having shock in their study which was lower in frequency to our study.

In a study by Vivek Kumar et al (2014)[25] the frequency of hepatomegaly, splenomegaly and anaemia was 73%, 69% and 67% respectively. The finding of palpable liver and spleen was high in their study. This study was done from areas of Delhi and Chandigarh and they specifically segregated the patients of scrub typhus. Probably the large number of presence of spleen and liver in their study may be the reason for that. Twenty four (18.5%) of patients had respiratory findings in form of rhonchi, effusion and crackles in our study. Matthew R. Kasper et al (2012)[7] also had predominant symptoms of influenza like illness but he did not mentioned presence of physical signs of chest.

Our hospital had a specific laboratory facility for diagnosis of scrub typhus. Detailed search for clinical evidence of eschar was done in the present study. The eschar was found in 10 (7.7%) of patients in our study group. All these patients were later on found to be positive for IgM scrub typhus. Vivek Kumar et al (2014)[25] found 12% incidence of scrub typhus in their study. The presence of eschar was highlighted in the study of Vivek Kumar et al (2014).[25] Eight (6.2%) and 3 (2.3%) of patients had impaired consciousness and neck rigidity in our study. These patients were investigated for the presence of inflammatory brain diseases but not a single patient of inflammatory brain disease was found.

Etiological diagnosis

Septicemia with or without shock with MODS : The maximum number of patients 95 (73.07%) were having septicemia with or without shock and multiorgan failure. In a study from South India Zabiuddin et al (2018)[26] reported septicemia in 161 (70%) cases. However he divided the patients of septicemia into community acquired and hospital acquired groups whereas in present study hospital acquired septicemia were not taken. S Saravanan et al (2017)[27] reported sepsis as a cause of AKI in his study but he did not exactly mention the number of cases of septicemia.

Malaria : Malaria was the second common etiological factor in present study 38 (29.2%). Dr. Atishay Jain et al (2018)[28] reported AKI with AFI from Malwa region, Indore. He reported about 25% of malaria in his study. Similar data has been given by S Saravanan et al (2017)[27] Zabiuddin et al (2018)[26] Vivekanand Jha et al (2013)[29]. All these studies were from south, north

and central part of India. This highlights the fact that probably all parts of India are more or less prone to have malaria irrespective to their geographical location.

Dengue : In the present study 22(16.9%) of cases of dengue were seen. About 54% of cases noted by JayalalJayapalan Nair et al (2016)[30] and only 8.4% cases were reported by Matthew R. Kasper et al (2012)[7] . They had common history of poor fluid management prior to coming to our hospital. Only 6% cases of dengue were reported by Sriram Krishnamurthy et al (2012)[31]. This study was from south India and therefore less number of patients of dengue were expected in their study.

Pneumonia : Twenty (15.4%) of pneumonia cases were seen in present study. Comparable 26% patients of pneumonia with AKI was reported by Sriram Krishnamurthy et al (2012)[31] from south India.

Scrub Typhus : The present study had 12 (9.2%) cases of scrub typhus. Out of 12, 10 (7.69%) of patients had eschar and 2 (1.5%) cases were diagnosed on the basis of serological tests. JayalalJayapalan Nair et al (2016)[30] reported only 2 (7%) cases in his study. Basu G et al (2007)[32] reported 51.2% cases from southern India. Their scrub typhus patients were very high from the present study. A geographical difference may be the reason for that.

Acute Gastroenteritis : In present study 15 (11.5%) cases of AGE were found. Out of which all patients had shock. Whether the AKI was direct consequence of infective diarrhea or it was secondary to the hypoperfusion of kidney was not clear. Sriram Krishnamurthy et al (2012)[31] reported 17% of cases of AKI due to diarrhea but his study was done in the childrens in year 1990. The incidence of diarrhea with AKI is declining with time[33].

Urosepsis : Twelve (9.2%) cases of urosepsis were seen in our study. They were diagnosed on the basis of symptoms of LUTS with findings of presence of infection in urine analysis and culture. K Mehta et al (2018)[23] studied 1% cases with urosepsis. Most of the studies JayalalJayapalan Nair et al (2016), Sriram Krishnamurthy et al (2012) and Basu G et al (2007) did not report the urosepsis as a cause of AKI.[30-32]

Tuberculosis : Six (4.6%) of tuberculosis were seen in present study. They all were having features of dissemination and their blood pressure was low. Probably they had renal failure secondary to the hypoperfusion of the kidney.

Enteric fever : Six (4.6%) cases of enteric fever was seen in present study. Their diagnosis got made on the basis of spleen and blood culture. K Mehta et al (2018) also reported 3.5% cases of enteric fever in his study[23].

Undiagnosed : We had 13 (10%) cases undiagnosed in our study. The serological tests for the leptospirosis and chikungunya were not done in present study. Many undiagnosed and unknown viral diseases like hanta virus infection, other rickettsial spotted fever are described in literature which we were unable to workup in present study.[32]

The another reason for not identifying organism is due to lack of sophisticated diagnostic facilities. This fact was also highlighted by S. Saravanan et al (2017).[27]

Classification of renal failure

In our study most common cause of AKI was pre renal failure AKI i.e. 98 (75.4%) and shock was the most common etiology 98 (75.4%) for that. The cause of shock was sepsis, acute gastroenteritis, tuberculosis, malaria and dengue 29 (29.6%), 15 (15.3%), 6 (6.1%), 30 (30.6%), 18 (18.4%) respectively. In intrinsic renal causes of AKI maximum number of cases were seen by malaria 8 (25%) followed by scrub typhus, dengue

and MODS in 6 (18.8%),4 (12.5%) and 4 (12.5%) cases respectively. Post renal causes were mostly surgical. Surgical causes were our exclusion criteria so post renal causes of AKI were not included in our study. James Kaufman et al reported 70% of the patients had prerenal azotemia, 11% with intrinsic acute renal failure and 17% with obstruction. He was unable to classify 2% patients.[34] P value was statistically significant in our study (p value <0.05).

Classification of renal failure and etiologies

In the present study total 98 patients were having shock. Etiologies which contributed to shock were sepsis, AGE, tuberculosis, malaria and dengue in 29 (22.30%), 15 (11.5%), 6 (4.6%), 30 (30.6%) and 18 (18.4%) cases respectively. It was observed that rest of the cases were not having shock in these etiologies. Those patients who were having renal failure without shock were the result of direct renal injury to the kidney by primary infective diseases.

Severity of renal failure

Patients were classified into 3 groups of severity on the basis of serum creatinine level and urine output :

1. Mild 2) Moderate 3) Severe

In present study most of the cases of malaria and scrub typhus included in the category of severe renal failure i.e. 20 (15.4%) and 12 (9.2%) respectively. Moderate renal failure had mixed overlapping of tuberculosis, acute gastroenteritis, pneumonia and undiagnosed cases. Moderate renal failure was seen in malaria, pneumonia, tuberculosis, AGE and undiagnosed cases of 12 (9.2%), 10 (7.8%), 2 (1.5%), 6 (4.6%) and 5 (3.8%) respectively. Dengue, pneumonia, urosepsis and few numbers of tuberculosis, AGE, enteric fever and undiagnosed cases caused mild renal failure.

In the study by JayalalJayapalan Nair et al (2016)[30] malaria was the cause of 50% of cases of severe renal failure which was almost equal to our study. Basu G et al (2011)[32] also studied scrub typhus (51.2%) as a cause of severe renal failure. In his study enteric fever (8.7%) was seen with mild renal failure. The insult to the kidney is from multiple sites in cases of malaria i.e. shock, hemolysis, stagnant flow in renal tubules and release of vasoactive nephrotoxin chemical mediators. This explains the severe renal failure in cases of malaria in the present and as postulated in various other studies.

Conclusions

This study was conducted in Department of General Medicine, Dr. Susheela Tiwari Government Medical College and Hospital, Haldwani between September 2017 to August 2019. The following conclusions were made:

1. Acute febrile illness with AKI were seen more with the advancing age. Anatomical and physiological changes that occur in the kidney with advancing age might be the reason for that in elderly patients. The gradual reduction in functional nephrons with advancing age makes a person more susceptible for early renal involvement.
2. The percentage of males was more in comparision to females.
3. Malaria, dengue, scrub typhus, pneumonia and AGE maximally contributed to the AKI.
4. Mortality was zero and none of patients required renal replacement therapy in present study.
5. Early and meticulous treatment for restoration of circulatory volume, correction of electrolytes, acidosis and early initiation of specific treatment was the reason that all the patients of present study were managed successfully by conservative treatment.

6. The empirical and judicial use of anti-malarials and doxycycline was done in case of undifferentiated fever in present study. Their use in remote settings where the sophisticated lab facilities were not available is a matter of futher consideration.

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