Acute Kidney Injury with Hemolytic Uremic Syndrome

A single center experience

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Abstract:

Aim: We report here, case series of patients with acute kidney injury (AKI) developing in association with hemolytic uremic syndrome (HUS). Different causes of HUS and outcome of patients in this group of patients is aimed to be reported.

Patients and Methods: subjects for the study reported here comprised of a cohort of 105 patients admitted with the diagnosis of AKI due to HUS. AKI was defined according to RIFLE criteria and HUS on basis of hematological, biochemical and/or histological features. All patients had normal size kidneys on ultrasonography and no previous co- morbidity.

Results: One hundred and five patients with AKI due to HUS were brought to this institute from January 2000 - July 2019; among these 76 were females, mean age of these patients was 27.83 ± 10.50 years. Causes of HUS were febrile illness, with or without diarrhea, diarrhea alone, pregnancy related complications and one each from snake bite, HCV infection / IFN therapy and use of combination of drugs. In pregnancy related HUS one patient had HUS during pregnancy while rest were during postpartum. Renal replacement was required in 95.23 % patients. Complete renal recovery was observed in 22 patients, while 15 died during acute phase of illness. CKD-V developed in 24 patients, 41 patients lost long term follow up, but were dialysis free till last follow up. Treatment with plasmapheresis revealed significantly better renal recovery (p value 0.026) in this group of patients.

Conclusion:

HUS can be severe life threatening disease; AKI with background of HUS may remain irreversible in many of these patients. Plasmapheresis should be offered to patients with established diagnosis of HUS.

Key Words: AKI, RIFLE criteria, Hemolytic Uremic Syndrome, Plasmapheresis.

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Introduction:

Hemolytic uremic syndrome (HUS) is a rare and severe form of thrombotic microangiopathy associated with a poor renal prognosis. The syndrome is characterized by the combination of mechanical hemolytic anemia, thrombocytopenia, and acute kidney injury.¹ HUS arises from an insult to endothelial cells which may result from one of these pathogenic mechanisms:

1. verotoxin-induced endothelial cell activation and apoptosis, in Shiga toxin induced HUS.
2. acquired or constitutional complement alternative pathway dysregulation which results in endothelial cell damage (atypical HUS)
3. secondary HUS associated with infections, drugs, autoimmune diseases or pregnancy. All reveal well-defined patterns of endothelial cell lesions.²

Among pregnant patients presenting with thrombotic microangiopathies, Thrombotic Thrombocytopenic purpura (TTP) due to ADAMTS13 deficiency is more common presentation than HUS.^{3,4} In the presence

of other associated complications with pregnancy, such as preeclampsia, HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome, and/or in some instances severe postpartum hemorrhage, the diagnosis of pregnancy associated HUS can be difficult.^{5,6}

Complement pathway dysregulation ultimately causing complement 5 activation in the development of atypical HUS is well established now identification of complement pathway dysregulation especially complement 5 playing a major role in. It has been speculated that, complement alternative pathway dysregulation combined with specific precipitating events can lead to pregnancy associated HUS (P-aHUS).^{4,7,8}

We hereby aim to report our experience of acute kidney injury (AKI) associated with HUS, including all forms of HUS over about twenty years. This series will highlight frequency of different causes of HUS in our adult population and its outcome (both renal and patient survival) in this particular population.

Patients and Methods:

In this retrospective study we reviewed clinical records of all adult patients (≥ 18 years) who were admitted to Sindh Institute of Urology and Transplantation (SIUT) between January 2000 – July 2019 and in whom the diagnosis of AKI secondary to HUS was established.

In this study AKI was defined according to RIFLE criteria;⁹ i.e.

Risk: when serum creatinine increased 1.5 times from base line or urine output decreased to less than 0.5/kg/ hour over previous 6hours.

Injury: when serum creatinine increased 2 times from base line or urine output decreased to less than 0.5/kg/ hour over previous 12 hours.

Failure: when serum creatinine increased 3 times from base line or creatinine $> 4\text{mg}\%$ or urine output decreased to less than 0.3/kg/ hour over previous 24 hours, or anuria over past 12 hours.

Loss: when complete loss of renal function for > 4 weeks.

All patients in present study fell in one of the categories from Injury to Loss, at time of arrival to this hospital (as some obstetric patients referred early because of decline in urine output).

US was defined as association of following criteria: mechanical hemolytic anemia (hemoglobin < 11 g/dl, raised lactate dehydrogenase, presence of schistocytes or fragmented red blood cells on blood peripheral film) and thrombocytopenia (platelet count $< 150 \times 10^3/\mu\text{l}$). During initial period of study that is between 2000-2004 renal biopsy was not performed in all patients but during later part (from 2005 onwards) all patients had renal biopsy done and diagnosis of HUS was confirmed on biopsy along with other criteria of fragmented RBC, extravasations of red blood cells, obliteration of capillary lumina and presence of fibrin thrombi. Patient demographics were recorded for laboratory parameters of CBC, renal chemistry, liver function tests, coagulation profile, urinalysis, serum LDH and complement levels. Factor H; which is done by ELISA method in our laboratory was available for patients who were registered after March 2015. Management of all patients was recorded for need for renal replacement therapy (RRT), plasmapheresis, its duration and finally outcome. Only data from patients fulfilling criteria of definitions for AKI and HUS, be it hematological/ biochemical or histological, were included in the study.

All patients were followed up till death, complete renal recovery or no recovery (labeled as CKD-V), except three patients who refused treatment and got discharged from hospital against medical advice. Patients with partial recovery of kidney function and who lost to follow up were considered among the partial recovery of patients.

Statistical methods:

Statistical analysis was done on SPSS version 20.0 (IBM, USA). Mean $\pm$ standard deviation was expressed or median with inter-quartile range provided for continuous variables. Frequencies and percentages computed for categorical variables. For comparison of mean difference one way ANOVA was used and chi square test was used to determine the proportional difference between outcomes with

different presenting symptoms or outcome with provision of plasmapheresis. P value <0.05 was considered as significant.

Results:

During the studied period from January 2000 – July 2019, total 105 patients were diagnosed to have AKI secondary to HUS. Among them 76 were female and 29 male with median age of 25 years. Basic demographics of studied population and initial laboratory parameters are given in table 1.

Table1: Baseline demographics and laboratory values among 105 Hemolytic Uremic Syndrome patients.

Parameters	Mean $\pm$ SD	Median	Inter Quartile Range
Age (years)	27.83 $\pm$ 10.50	25	20-33
Duration of Insult (days)	12.09 $\pm$ 10.13	9	5.25-14
Hemoglobin (G/dL)	7.44 $\pm$ 1.83	8	6-9
Total leukocyte count	15.73 $\pm$ 9.44	11	9.5-21
Platelet $\times 10^3/\mu\text{l}$	119.89 $\pm$ 97.54	90	54.50-155
Urea (mg/dl)	210.70 $\pm$ 97.72	186	147.50-269
Creatinine (mg/dl)	9.96 $\pm$ 4.14	9	7-12
LDH (U/L)	2222.09 $\pm$ 1254.47	1878	1311-2869.25
Factor H(mcg/ml)	895.61 $\pm$ 329.74	952	644-1115
Ref range 250-600			
C3 g/L -0.69	0.8651 $\pm$ 0.32	0.87	0.67-0.99

Common presenting symptoms were fever alone, fever associated with diarrhea, fever associated with neurological symptoms, diarrhea alone or pregnancy related problems which included preeclampsia, antepartum or postpartum hemorrhage, intra uterine fetal demise, postpartum eclampsia or during pregnancy in one patient, Table 1. One patient each had HUS after snake envenomation, hepatitis C positive patient who was on interferon therapy and another patient after taking combination of anxiolytic drugs developed HUS. Decline in urine output was reported in 88 (83.80%) patients, of these 40 were anuric and rest oliguric. Non oliguric AKI was present in 17 patients, Figure 1. Time from first day of symptom to reaching to our hospital was recorded as days of insult and given in Table 1. Raised serum bilirubin $\geq$ 2mg/dl was found in 17 (16%) patients, while raised liver enzymes were reported in 43 (41%) patients. Among those who were able to provide sample for urinalysis, 76 (72.38%) had microscopic hematuria and 1-3+protein on dipstick was recorded in 69 (65.7%) and 4+ protein in 7 (6.66%). Deranged International Normalized Ratio (INR) (1.6 – 3.91) was found in 9 patients at time of admission.

Renal replacement therapy was required in 100 (95.23%) patients, 2-14 sessions of hemodialysis was done in those who either completely or partially recovered or died during acute phase of illness, in CKD – V it continued beyond 12 weeks at last follow-up. Plasmapheresis was done in 63 (60%) patients; 2-22 sessions were done, among these were 23/63(36.5%) who had P-aHUS.

Outcomes in patients with different presenting symptoms are tabulated in table 2. In terms of mortality during acute stage of illness it was significantly higher in other groups when compared with P-aHUS and AKI (p value 0.007). It was observed that renal recovery was significantly better in patients who were provided with plasmapheresis (p value 0.026). Time duration from first symptom to reaching at this facility did not show significant difference in patient outcome (p value 0.767).

Figure 1: Urine output status classifying the 105 hemolytic uremic patients with anuric, oliguric and non oliguric Acute Kidney Injury (AKI)

Discussion:

Over last one and half decade with better understanding of the pathogenic mechanisms underlying aHUS there is now more understanding towards disease-specific targeted treatment for these patients. However, high quality clinical trials to guide treatment for HUS are still lacking. The targeted inhibition of the complement alternative pathway became a promising treatment option for these patients, as constitutional (mutations in complement factor H, factor I, membrane cofactor protein, complement factor B, and C3 genes) or acquired (anti- factor H antibodies) dysregulation of the alternative C3 convertase emerged as a major risk factor for aHUS.^{1,5,10}

First complement inhibitor, the anti-C5 monoclonal antibody, eculizumab has been used in the management of aHUS.^{11,12} This is a humanized monoclonal antibody that inhibits the production of the terminal complement components and the membrane attack complex C5b-9 by binding to complement C5. It also blocks the pro-inflammatory and cytolytic effects of terminal complement activation.¹³ The use of Eculizumab is limited for the reasons of non availability at many countries and its high cost.

Previously plasma exchange was suggested first line therapy for typical HUS associated with severe renal insufficiency or brain impairment and early plasmapheresis, with or without eculizumab, was supposed to remain the cornerstone of treatment.¹⁴

Some studies done before the Eculizumab trials, have reported Plasmapheresis (PP) as the most effective treatment.^{15,16} PP replaces functionally defective proteins and removes overactive proteins and should be started earlier once the diagnosis is suspected, recommendations are to replace 1 to 2 plasma volumes in adults and 50 to 100 mL/kg in children with each treatment. Some would recommend continuing PP till the thrombotic microangiopathy (TMA) is controlled. In those patients who respond, PP can be gradually withdrawn, although a significant proportion will require continued PP to maintain remission.¹⁷

Table 2: Outcomes with different presenting symptoms of 105 patients with diagnosis of hemolytic uremic syndrome.

Symptom (n)	Recovered (22)	Partially Recovered (41)	CKD-V (24)	LAMA (3)	Died (15)
Fever (36)	7	21	6	0	2
Diarrhea (12)	0	6	1	0	5
Fever + Diarrhea (18)	6	2	1	2	7
Fever + Neurological Symptoms (4)	1	1	1	0	1
Pregnancy Related (32)	8	10	13	1	0
Others (3)	0	1	2	0	0

In a study based on Lanark shire Escherichia coli outbreak, it was reported that mortality was reduced in older patients treated with PP.¹⁸ In present study which is analysis of retrospective data, many patients were not considered for plasmapheresis (especially during early part of study), reason for which is not clear in records but it was evident that those who were offered this therapy revealed statistically significant better renal outcome (p value 0.026).

P-aHUS refers towards the thrombotic microangiopathy resulting from uncontrolled complement activation during pregnancy or the postpartum period. This is a devastating disease where clinical understanding and treatment options are still limited.¹⁹ P-aHUS may develop as a complication of pre-eclampsia,²⁰ in association of HELLP syndrome or sometimes with extensive peripartum hemorrhage.⁵ Some women progress to life threatening variant of preeclampsia with severe microangiopathic hemolytic anemia and thrombocytopenia along with AKI and liver damage. In this situation coagulation may be found to be abnormal with disseminated intravascular coagulation.²¹ In a study in 2014 from Rawalpindi, Pakistan, among pregnancy associated AKI 13/88(15%) had HUS, however their outcome was not mentioned.²²

In another recent study from Karachi, Pakistan, among 111 patients with pregnancy associated AKI, 7 were diagnosed with HUS and among them 3 had concomitant preeclampsia also.²³ However no further data related to morbidity and mortality was mentioned. In the present study among the 32 patients who had P-aHUS, only 8 (25%) had complete recovery and 23 (72%) had either partial recovery or required dialysis, Table 2. Treatment of P-aHUS needs Eculizumab (AntiC5 Antibody), which is not available in Pakistan. It is likely that early diagnosis and intervention with early delivery and management of sepsis etc. and possibly plasma exchange in rapidly deteriorating kidney function could halt the complement activation.²⁴

Atypical HUS can occur at any age, primarily affecting children of less than two years. Reported outcome of atypical HUS is poor, around 25% of the patients die during the acute phase and 50% require long term dialysis.²⁵ In present study we found 14.3% mortality during acute phase, 23% requiring long term dialysis and in another 39% patients confirmed fate cannot be commented, though they were in recovery phase when seen on last visit to hospital but not yet fully recovered, while 21% patients have shown complete renal recovery documented at long term follow ups.

Limitations of study:

As study is based on clinical data from a patient population at a tertiary renal care unit, patients usually referred here with established renal failure and all those who had febrile illness alone or diarrhea alone or combination of symptoms, most of these initial symptoms already settled thus stool cultures were not sent for most of these patients. ADAMTS 13 activity was not tested in studied population. ELISA based assay for assessment of factor H was available in 41 of 105 patients as during initial period of study this assay was not available. Genetic screening and testing for autoantibodies were not performed in these patients.

Conclusion and Recommendations:

Despite limitations with current study it is evident from data that prognosis in terms of renal recovery is not very good in AKI associated with HUS, timely determination of cause of HUS and targeted therapy may help improving the outcome. It is thus important to know the burden of disease so that future diagnostics and treatment modalities can be planned in accordance.

Conflict of Interest: None

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