Original Article

# Characteristics and outcome of hemolytic uremic syndrome in Sudanese children in a single Centre in Khartoum State

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## ABSTRACT

Hemolytic uremic syndrome (HUS) is one of the important causes of acute kidney injury (AKI) and chronic kidney disease (CKD) in children. Proposed prognostic features are controversial. We reviewed, retrospectively, the records of children with HUS seen at Soba hospital, Khartoum (2004-2012). We aimed to study demographics, clinical/laboratory features, outcome and prognostic risk factors. Thirty-nine children with HUS were recorded; 59% had diarrhoea positive (D+) and 41% diarrhoea negative (D−) HUS. The mean age was 65.4 months and males were 61.5%. At the acute phase seizures, coma, anuria/oliguria and hypertension were present in 25%, 17.9%, 51.3% and 53.8% respectively. Severe anaemia, thrombocytopenia, and leukocytosis were present in 71.8%, 97.4%, and 28.2% respectively. On discharge, hypertension was detected in 23.1%. Clinical and laboratory features were not significantly different in D+ and D− cases ($P > 0.05$ for all parameters). Dialysis was undertaken in 84.6% and acute mortality was 12.8% being significantly higher in D+ ($P = 0.002$). Demographic, clinical and laboratory features, late referral or need for dialysis were not significantly associated with higher risk of acute mortality ($p > 0.05$ for all). At short-term follow up (mean period ± SD of 18.54 ± 13.21 months), 51.3% had complete renal recovery, 15.4% CKD 3-4, 12.8% CKD 5 requiring renal replacement therapy (RRT), and 20.5% died. Higher mean serum creatinine and hypertension on discharge were risk factors for adverse outcome (CKD5 requiring RRT or death), $P = 0.011$ and 0.00 respectively. In spite of institution of RRT and supportive therapy, our data showed less favourable outcome of HUS.

**Keywords:**

Acute kidney injury, Chronic kidney disease, Children, Hemolytic uremic syndrome, Outcome, Sudan.

## INTRODUCTION

Hemolytic uremic syndrome (HUS) is among the important causes of acute kidney injury (AKI) and chronic kidney disease (CKD) in children [1]. The disease defined by the clinical triad of micro-angiopathic hemolytic anaemia, thrombocytopenia and AKI belongs to the group of thrombotic micro-angiopathies

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(TMA) [2]. Previous classifications according to clinical presentation have been challenged by recent concepts of aetiology and pathogenesis. D+ HUS has been used for HUS preceded by diarrhoea, which is usually due to Shiga-toxin producing Escherichia coli mostly 0157:H7 (STEC), whereas atypical HUS (aHUS) or D− has been used for the non STEC associated type [1]. D+ HUS is the commonest, has a relatively benign course, and usually does not relapse [3]. The aHUS or D− is less common, with tendency to relapse, and with a high risk of renal damage and death [4-6]. aHUS or D− may be primary (no cause, or familial due to complement dysregulation) or secondary to infectious or non-infectious causes [7]. Although the prognosis of D+HUS has improved but the overall prognosis of HUS is poor with high risk of CKD and death [8, 9]. High acute mortality rate, short and long term prognosis have been attributed to many risk factors including demographic, clinical, and laboratory features, and type of management [10-12]. However, findings in different reports have been controversial. Data about HUS Sudan is scanty. Our objective was to study the characteristics of HUS and determine short-term outcome and risk factors for prognosis in children followed in a single centre.

# METHODS

We retrospectively reviewed the records of all children with HUS who have been followed at the pediatric renal unit in Soba hospital, Khartoum, between August 2004 and August 2012. Criteria for diagnosis of HUS were the presence of the clinical triad of micro-angiopathic hemolytic anaemia, thrombocytopenia and AKI [2]. Patients with incomplete records were excluded. Data were abstracted from the records using standard data collection sheet. Personal data, history, height, weight, blood pressure, clinical course and outcome were recorded. Laboratory data including full blood count, serum creatinine, blood urea, serum electrolytes, and urine analysis were recorded. All relevant data were recorded at admission, discharge and at last follow up clinic visit. Results of the haematological data (Hb, TWBCs, and platelets count and reticulocyte count) and biochemical data (blood urea, serum creatinine, serum Na+, K+, $C^{2+}$ and $P^{o-4}$) were recorded as low or high levels if below or above the age gender-specific values respectively [13]. Acute kidney injury (AKI) was diagnosed on the basis of serum creatinine levels ≥150% above normal levels for age and oliguria (≤ 0.5 ml/Kg per hour for 6 hours) and/or occurrence of acidosis, and/or urea, phosphate and potassium outside the normal range for age [14]. CKD was defined as glomerular filtration (GFR) < 60 ml/min/1.73 $m^2$ for ≥3 months and CKD5 requiring RRT as GFR < 15 ml/min/1.73 $m^2$ [15]. Estimated GFR (eGFR) was calculated from the Schwartz formula [16]. Hypertension was defined as blood pressure higher than 95$^{th}$ percentile for age based on data from the Fourth Task Force Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescence [17]. Facilities for isolating STEC and performing compliment abnormalities were not available in our centre. We, therefore, used the terms D+ HUS and D− in our case definitions.

## Data analysis

Data entry and analysis was done using a Statistical package for social sciences (SPSS) version 15. Descriptive statistics such as means ± standard deviation (SD) were used for variables such as age and clinical and laboratory features. Percentages were used for categorical data. Variables were compared using student's t-test. Chi-square test was used to examine the association between risk factors during the acute phase of the disease, and acute mortality and adverse outcomes on follow up. P value less than 0.05 was as considered as statistically significant.

Ethical approval was obtained from the ethical committee in Sudan medical specialized board and Soba Hospital research committees. An informed consent was obtained from Soba Hospital Director.

# RESULTS

A total of 39 children with HUS (24 males; 61.5%) were recorded with a mean age ± SD at diagnosis of 65.47 ± 51.62 (range 4-168) months. Infants constituted 17.1% and those below five years 48.7% (Table 1). Most of the cases (61.5%) were referred from other states. HUS preceded by a prodrome of bloody diarrhoea (D+) was diagnosed in 23 cases (59%), D− in 16 (41%), but no familial HUS. The mean duration of symptoms ± SD was 10 ± 6.2 (range 1-28) days. We documented demographic, clinical and laboratory features and outcome during the acute phase in D+ and D− HUS

(Table 2). D+ patients had lower age at presentation than D− and that was statistically significant, P = 0.003. However, there was no statistically significant gender difference, P = 0.440. Seizures, coma, anuria/oliguria, and hypertension were present in 25%, 17.9%, 51.3% and 53.8% respectively. Severe anaemia (Hb < 5 gm/dl), thrombocytopenia, and leukocytosis were detected in 71.8%, 97.4%, and 28.2% of cases respectively. The mean haemoglobin ± SD was 5.7 ± 1.6 (range 3.6-9.5) gm/dl and the mean serum creatinine ±SD was 6.4 ± 3.4 (range 1.9-15) mg/dl respectively. On discharge, hypertension was detected in 23.1% and the mean high serum creatinine ±SD was 6.2 ± 2.8 mg/dl. Clinical and laboratory features were not significantly different in D+ and D− (P > 0.05 for all parameters), Acute mortality was recorded in 12.8% being significantly higher in D+ than D−, P = 0.002, table 2. Dialysis was undertaken in 84.6% and 15.4% were conservatively treated Dialysis modality was peritoneal dialysis (PD) in 54.5%, hemodialysis (HD) in 18.2% and both modalities in 27.3%. Supportive therapies used were transfusion of packed RBCs ± plate lets in 84.6% and fresh frozen plasma (FRP) in 12.8%. Risk factors for acute mortality were assessed (Table 3). There was no statistically significant association between acute mortality and demographic, clinical and laboratory features, late referral or need for dialysis (P > 0.05 for all parameters). Outcome at short-term follow up (mean period ± SD was 18.54 ± 13.21 months) is shown in table 4. Complete renal recovery, with a mean GFR of 110.82 ± 24.91 ml/min/1.73 $m^2$, was recorded in 51.3%, CKD 3-4, with a mean GFR of 27.08 ± 10.82 ml/min/1.73 $m^2$ in 15.4%, CKD5 requiring renal replacement therapy (RRT) in 12.8%, and death in 20.5%. Two patients who recovered normal function (5.1%) remained with permanent neurological sequels. There was no statistically significant association between hypertension at admission or need for dialysis and the risk of adverse outcomes (CKD5 requiring RRT or death), P = 0.336; Relative Risk [RR] = 1.81; 95% confidence interval [95% CI]; 0.49-6.68 and P = 0.677; RR = 1.47; 95% CI; 0.23-9.20 respectively. However, high mean serum creatinine and hypertension on discharge were risk factors for adverse short-term outcome, P = 0.011; RR = 8.16; 95% CI; 1.14-4.72 and P = 0.00: RR = 4.60, 95% CI; 2.11-9.98 respectively.

**Table 1 - Age distribution of children with hemolytic uremic syndrome in the study.**

| Age in years | Number | Percent |
|---|---|---|
| <1 | 7 | 17.9% |
| 1–5 | 12 | 30.8% |
| 5–10 | 11 | 28.2% |
| >10 | 9 | 23.1% |
| Total | 39 | 100.0% |

# DISCUSSION

The outcome and risk factors for prognosis of HUS were not adequately defined in many developing countries. This may be due to lack of resources, trained personnel, and data collection infrastructure. Establishment of a pediatric nephrology unit in 2004 in our hospital has improved our patient care and data registry. We took this opportunity to study the characteristics, outcome of HUS and the probable risk factors for prognosis. Over eight years, we managed 39 children with HUS. In a previous earlier report HUS was a rare cause of CKD (2%) [18]. This could be due to misdiagnosis or underreporting of cases at secondary care levels. However, in a recent report HUS was an important cause of AKI (8%) [19]. In this study, males were predominantly affected and D+ patients were younger than D− which is similar to other studies [20-22]. We diagnosed D− in 41% of patients compared to 25%-18.5% in other countries [10, 23, 24]. This may be due to lack of data about STEC or its underreporting in our community The demographic, hematological and biochemical findings in this study were comparable to other studies [10, 24]. Our acute mortality rate of 12.8% was higher compared to Western data (7.4%-1.5%), which may be due to the early detection and institution of supportive therapy in these countries [23, 25-28]. In contrast, our acute mortality was lower

compared to developing countries (12.8% versus 17.3%-24% respectively) [10, 24, 29]. In many studies high acute mortality was related to many factors e.g. late referral (>28 days), leukocytosis, hypertension at presentation, neurological manifestations and need for dialysis [10, 25, 26]. In contrast, in another study and in our study none of these factors were significantly associated with high acute mortality (P > 0.05 for all parameters) [24]. However, unrecorded co-morbidities e.g. fluid overload and severe acidosis might have a role in higher mortality. At short term follow up, 15.3% of our patients had CKD3-4. This result is comparable to reports in Iran (11%), Brazil (11.1%), and Argentina (16.1%), but lower than in South Africa (32%) [10,23,26,29]. In this study, 12.8% of cases reached CKD5 requiring RRT and 10.3% died. Our prevalence of CKD5 requiring RRT is higher compared to developed countries; France (5-10%), Argentina (3.4%), and South Africa (1.2%) [25, 26, 29]. In these countries most of patients with CKD5 have better access to renal transplantation so few patients remain on dialysis. Use of herbal medicine is a known medical practice in our community, which might be related to rapid progression to CKD. We could not prove this because none of our patients declared the use of herbs. Many risk factors for poor renal outcome on long term have been described e.g. age >2-3 years, male sex, hypertension, hemoglobin of >10 g/d, leukocytosis and high serum creatinine in the acute phase [30-32]. A meta-analysis from 18 countries showed 12% had CKD5 requiring RRT or died and concluded that CNS symptoms and need for early dialysis were predictors of poor outcome [33]. In this study, the overall mortality of 20.5% is far less than reported in other developing countries; India 60%, Kenya 55% [34, 35]. Our follow up period was relatively short and therefore conclusions could not be made about associations of these factors and poor long-term prognosis. However, at short-term follow up we found a significant association between high mean serum creatinine and hypertension on discharge and the risk of adverse outcome (CKD 5 or death). This finding is consistent with other studies [26]. However, we did not find statistical significant association between hypertension in the acute phase of the disease or need for dialysis and the risk of these adverse outcomes as shown in other studies [30-32].

**Table 2 - Demographic, clinical, and laboratory features and outcome of hemolytic uremic syndrome during the acute phase.**

| Characteristic | Study group (n = 39) | D+ HUS (n = 23) | D− HUS (n = 16) | P value |
|---|---|---|---|---|
| Mean age (months) | 65.47 ± 51.62 | 45.54 ± 44.73 | 94.12 ± 48.28 | 0.003* |
| Male/Female ratio | 1.3 | 1.3:1 | 2.2:1 | 0.440 |
| Seizures | 10 (25.0%) | 6 (26.0%) | 4 (25.0%) | 0.939 |
| Coma | 7 (17.9%) | 3 (13.0%) | 4 (25.0%) | 0.339 |
| Anuria/Oliguria | 20 (51.3%) | 12 (52.1%) | 8 (50.0% | 0.894 |
| Hypertension at admission | 21 (53.8%) | 12 (52.2%) | 9 (56.2%) | 0.802 |
| Severe anaemia | 28 (71.8%) | 15 (65.2%) | 13 (81.3%) | 0.270 |
| Leukocytosis | 11 (28.2%) | 7 (30.4%) | 4 (25.0%) | 0.711 |
| Thrombocytopenia | 38 (97.4%) | 22 (95.6%) | 16 (100%) | 0.398 |
| Mean Hb (gm/dl) at admission | 5.7. ± 1.6 | 6.06 ± 1.26 | 5.55 ± 1.26 | 0.460 |
| Mean high s. creatinine (mg/dl) at admission | 6.4 ± 3.4 | 6.36 ± 3.31 | 7.00 ± 3.70 | 0.578 |
| Hypertension on discharge | 9 (23.1%) | 5 (21.3%) | 4 (25.0%) | 0.812 |
| Mean high s. creatinine (mg/dl) on discharge | 6.2 ± 2.8 | 6.04 ± 1.95 | 6.71 ± 3.62 | 0.690 |
| Mortality in acute phase | 5 (12.8%) | 4 (17.3%) | 1 (6.30%) | 0.002* |

*P value is statistically significant.

Hb – Hemoglobin, D+ HUS – Diarrhea positive hemolytic uremic syndrome, D− HUS – Diarrhea negative hemolytic uremic syndrome.

**Table 3 - Risk factors for mortality in the acute phase in hemolytic uremic syndrome.**

| Characteristic | Non survivors (n = 5) | Survivors (n = 34) | P value |
|---|---|---|---|
| Mean age months | 38.20 ± 42.36 | 69.48 ± 52.17 | 0.210 |
| Gender; Males<br>Females | 3 (12.5%)<br>2 (13.3%) | 21 (87.5%)<br>13 (86.7%) | 0.940 |
| Seizures | 2 (40%) | 8 (23.5%) | 0.431 |
| Coma | 1 (20%) | 6 (17.6%) | 0.898 |
| Oliguria/anuria | 2 (40%) | 18 (52.9%) | 0.589 |
| Hypertension | 2 (40%) | 19 (55.9%) | 0.506 |
| Mean hemoglobin (gm/dl) | 6.06 ± 1.26 | 5.55 ± 1.26 | 0.460 |
| Leukocytosis | 1 (20%) | 10 (29.4%) | 0.662 |
| Thrombocytopenia | 5 (100%) | 33 (97.1%) | 0.698 |
| Mean high Serum creatinine (mg/dl) on admission | 6.04 ± 1.95 | 6.71 ± 3.62 | 0.690 |
| Late referral | 2 (40%) | 9 (26.5%) | 0.530 |
| Need for dialysis | 4 (80%) | 29 (85.4%) | 0.759 |

*P value is statistically significant.

**Table 4 - Short term follow up outcome of patients with hemolytic uremic syndrome (n = 39).**

| Outcome | D+ HUS | D− HUS | Total | Percent |
|---|---|---|---|---|
| Complete renal recovery | 14 | 6 | 20 | 51.3% |
| With permanent CNS damage | 1 | 1 | 2 | |
| CKD3-4 | 3 | 3 | 6 | 15.4% |
| CKD5 requiring RRT | 2 | 3 | 5 | 12.8% |
| Death | 4 | 4 | 8 | 20.5% |
| Total | 23 | 16 | 39 | 100.0% |

CKD – Chronic kidney disease, D+ HUS – Diarrhea positive hemolytic uremic syndrome, D− HUS – Diarrhea negative hemolytic uremic syndrome, RRT – renal replacement therapy.

Efforts to improve outcomes may include the following; (a) earlier referral, (b) better diagnosis with identification of STEC, (c) early dialysis support, (d) plasma exchange, (e) avoiding co-morbidities, (f) better detection of familial complement deficiencies as clinical trials have shown that eculizumab to be more efficient than plasma therapy in a HUS due to complement dysregulations [31]. Plasma exchange, recently introduced in our Unit, may give support to D− patients despite controversy [32].

# CONCLUSIONS

In our cohort, the acute mortality and the adverse outcomes (CK5 requiring RRT and death) at short term were higher than in the Western countries but comparable to or even better than most of the developing countries having similar setting of renal services. High serum creatinine and hypertension on discharge were predictors for adverse outcome at short term. Our data indicate the need for better management facilities and further studies to define other etiologies, especially for D−, and risk factors for acute mortality and long term outcome. The continuous support from Sudan PD program, Sudan National Centre for Kidney diseases and Transplantation and IPNA training program would hopefully improve management and outcome of HUS. Microbiological facilities are now available in some of our laboratories and that would allow early and better diagnosis and identification of STEC.

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