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ORIGINAL ARTICLE

Duration of oliguria and anuria as predictors of chronic renal-related sequelae in post-diarrheal hemolytic uremic syndrome

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Abstract Prior long-term retrospective studies have described renal sequelae in 25–50% of postdiarrheal hemolytic uremic syndrome (HUS) survivors, but the ability to predict the likelihood of chronic renal-related sequelae at the time of hospital discharge is limited. We surveyed 357 children in our HUS registry who survived an acute episode of post diarrheal HUS (D+HUS) and were without end-stage renal disease (ESRD) at the time of hospital discharge. Of the 357 patients surveyed, 159 had at least 1 year (mean 8.75 years) of follow-up. Of these, 90 individuals were identified as having had at least 1 day of oliguria, with 69 individuals having had at least 1 day of anuria. The incidences of renal-related sequelae [proteinuria, low glomerular filtration rate (GFR), and hypertension] were determined among experimental groups based on oliguria and anuria duration. One or more sequelae (e.g. proteinuria, low GFR, hypertension) was seen in 25 (36.2%) of those who had no recorded oliguria and 34 (37.8%) of those with no recorded anuria. The prevalence of chronic sequelae increased markedly in those with more than 5 days of anuria or 10 days of oliguria, with anuria being a better predictor than oliguria of most related sequelae. A particularly high incidence of hypertension was seen in patients with > 10 days of anuria (55.6%) in comparison with those with no anuria (8.9%) [odds ratio (OR) 12.8; 95% confidence interval (CI) 2.9–57.5]. Patients with > 10 days of anuria were also at substantially increased risk for low GFR and proteinuria (OR 35.2; 95% CI 5.1–240.5). These findings may help identify children who need periodic and extended follow-up after hospital discharge.

Keywords Hemolytic uremic syndrome · Shiga toxin · *Escherichia coli* · Acute renal failure · Long-term prognosis

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Introduction

Postdiarrheal (Shiga-toxin mediated) hemolytic uremic syndrome (HUS) is the most frequent cause of acute renal failure in infants and young children [1]. Some patients who survive diarrheal HUS (D+HUS) never recover renal function, and others experience secondary decline in renal function years after apparent recovery [2–7]. Although the presence and duration of oliguria and anuria during the acute phase of HUS have been shown to correlate with long-term outcome, there is still a need for noninvasive ways to quantify the risk at time of hospital discharge. Being able to predict future renal sequelae at the time of hospital discharge would allow parents, patients, and doctors the opportunity to plan and prepare for future monitoring and treatment.

Methods

We utilized our computerized HUS registry to identify patients with post-D+HUS from 1970 to 2003. A case of classic D+HUS was defined as a child younger than 18

years of age with a prodrome of gastroenteritis (usually with hemorrhagic colitis) followed by microangiopathic hemolytic anemia, thrombocytopenia, and acute nephropathy [2]. For this study, oliguria was defined as urine output <240 ml/m^2 per day. Thus patients that were anuric were also included in the oliguria patient cohort. Anuria was defined as urine output <15 ml/day. Cases were not excluded because of a normal platelet count (i.e. > 150×10^9/L) because thrombocytopenia has not been documented during hospitalization in all cases of D+HUS. Thirteen patients who displayed end-stage renal disease (ESRD) at time of discharge and those who died (17 patients) during the acute phase of the disease were excluded from analysis. Of the 357 patients identified, 159 (77 males, 82 females) had at least 1 year of follow-up data; 90 of these had at least 1 day of oliguria. Sixty-nine patients, a subset of those with at least 1 day of oliguria, also had at least 1 day of anuria.

Patient information from our follow-up database was included only if it had been collected at least 1 year following hospital discharge. Individuals were separated into experimental groups based on absence, presence, and duration of oliguria and anuria, and the percentage of those with renal-related sequelae within these groups was determined. Sequelae of interest included proteinuria, glomerular filtration rate (GFR), a combination of proteinuria and low GFR, and hypertension. Proteinuria was defined as ≥1+ by dipstick analysis [8–10]. GFR was calculated by the Schwartz formula, with <90 ml/min per 1.73 m^2 being classified as an abnormal value [10–12]. Hypertension was defined as blood pressure >95th percentile for age and gender [9, 10, 13]. Urine measurements at follow-up were made using first-morning specimens.

Statistical analysis

Categorical variables were compared by Yates correct chi-square and Fischer exact tests. Continuous variables were compared by the Mann–Whitney tests. Analysis to compare those with follow-up information and those lost to follow-up was performed using the appropriate statistical tests for continuous and categorical variables. All statistical analysis was performed using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). To better define the contribution of the duration of oliguria and anuria to renal sequelae, binary logistic regression models were developed for each renal sequelae. Patients were divided into one of the following four cohorts: (1) no oliguria or anuria, (2) 1–5 days, (3) 6–10 days, (4) >10 days. The same acute-phase variables used in the ungrouped analysis were also entered into the logistic models. The models were adjusted to evaluate for differences in ascertainment or therapy by controlling for the decade of treatment and the length of follow-up. Two sided p values < 0.05 were considered significant. The reported odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated in reference to patients with no oliguria or anuria unless otherwise noted.

Results

One hundred and fifty-nine cases that met the criteria for inclusion in this study were identified from the computerized registry. The mean interval from hospitalization until study enrollment was 8.75 (range 1–30) years. The mean duration of oliguria was 9.2 days [standard deviation (SD)

Table 1 Demographic and clinical characteristics of patient population groups during acute-phase hospitalization

	No oliguria		≥ 1-Day oliguria		*P* value
	69	%	90	%	
Gender					
Female	39	56.5	43	47.8	0.274
Male	30	43.5	47	52.2	
Age distribution during acute phase					
0–2	42	60.9	61	67.8	0.437
3–4	11	15.9	14	15.6	
5–9	11	15.9	7	7.8	
10–17	5	7.2	8	8.9	
Hemodialysis	4	5.8	17	18.9	0.016
Peritoneal dialysis	6	8.7	65	72.2	< 0.001
Mean value ± standard deviation					
White blood count - admission (×10^9/L)	18.5±14.5		24.3±14.2		0.041
Hematocrit - admission (%)	19.1±4.1		17.2±3.0		< 0.001
Creatinine - admission (mg/dl)	3.2±2.9		7.4±4.0		< 0.001
Blood urea nitrogen - admission (mg/dl)	80.1±50.4		131.0±55.0		< 0.001
Platelets - admission (×10^9/L)	69.9±90.3		43.9±28.8		0.017

Table 2 Incidence of renal-related sequelae summarized by gender

	Female		Male		*P* value
	68	%	63	%	
Proteinuria	14	17.1	14	18.2	0.509
Low GFR	18	22.0	33	42.9	0.005
Hypertension	9	11.0	13	16.9	0.359
Low GFR and proteinuria	5	6.1	8	10.4	0.392
Any complications	31	37.8	43	55.8	0.026

GFR glomerular filtration rate

8.8 days; range 1–57 days], and for anuria 6.0 days (SD 4.9 days, range 1–24 days). There were no statistically significant differences for variables associated with hospital admission by decade of hospitalization (1970s, 1980s, 1990s, 2000s). No significant differences in acute-phase variables between those lost to follow-up and those included in analysis were detected. A moderately elevated incidence of sequelae was noted in patients with extended periods of follow-up. Follow-up duration was therefore entered in all multivariate models.

Table 1 provides demographic characteristics and selected clinical features of the study population during the acute phase of HUS. Statistically significant differences were noted in white blood cell count (WBC), hematocrit (HCT), blood urea nitrogen (BUN), serum creatinine concentration, and platelet counts in patients with no oliguria versus those with ≥ 1 day of oliguria. Statistically significant differences were also noted in the number of patients who received hemodialysis and those who received peritoneal dialysis. A relatively larger proportion of male patients suffered at least 1 day of oliguria (52.2%) in comparison with those with no oliguria (43.5%), though this difference failed to reach statistical significance. Table 2 shows the incidence of renal-related sequelae summarized by gender. Male patients exhibited an increased risk of low GFR in comparison with female patients. This difference persisted in multivariate models when controlling for age at admission and for length of follow-up.

Figure 1 shows the incidence of long-term renal-related sequelae and the relationship to oliguria duration. Figure 2 shows the incidence of long-term renal-related sequelae and the relationship to anuria duration. Patients with longer oliguria duration (> 10 days) exhibited higher incidence of all renal-related sequelae. The same trend was noted among patients with more than 5 days of anuria, though the overall incidence of sequelae was higher than that seen in patients with oliguria.

One or more sequelae (e.g. proteinuria, low GFR, hypertension) were seen in 25 (36.2%) of those who had no recorded oliguria and 34 (37.8%) of those with no recorded anuria. Tables 3 and 4 provide ORs of renal-related sequelae and their relationship to oliguria (Table 3) and anuria (Table 4) duration.

In the oliguric group, the incidence of patients with one or more sequelae remained fairly constant in patients with 1–5 days (39.5%; OR 1.2, 95% CI 0.5–2.6) and 6–10 days (36.4%; OR 1.0, 95% CI 0.4–2.7). A dramatic increase in the incidence of one or more sequelae to 88.7% (OR 11.4, 95% CI 3.6–36.5) occurred among patients with > 10 days of oliguria, however. Oliguria duration of > 10 days was

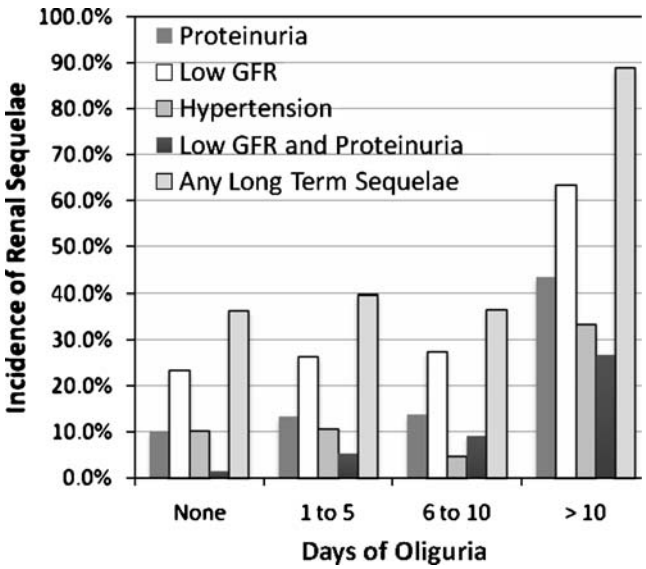

Fig. 1 Incidence of long-term renal-related sequelae versus days of oliguria. A large increase in the incidence of all sequelae occurs at > 10 days of oliguria

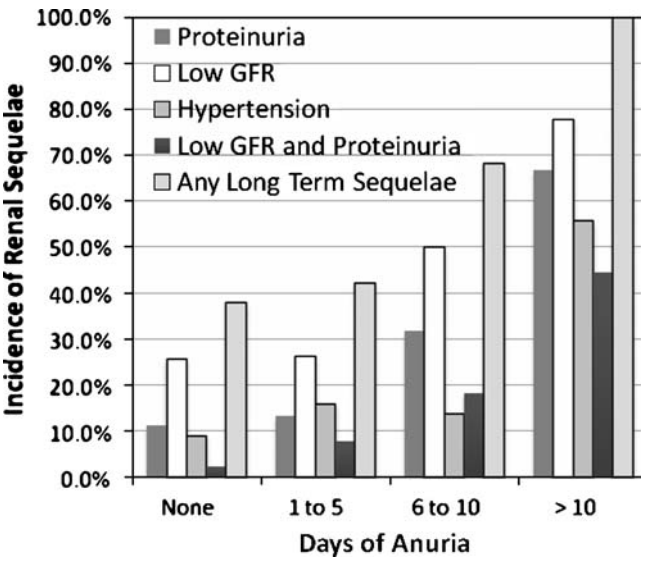

Fig. 2 Incidence of long-term renal-related sequelae versus days of anuria. Patients with longer durations of anuria exhibit higher incidence of renal-related sequelae

Table 3 Relationship between oliguria duration (in days) and the risk of long-term renal-related sequelae

Duration of oliguria (days)	None		1–5 Days			6–10 Days			> 10 Days		
	69	%	38	%	OR (95% CI)	22	%	OR (95% CI)	30	%	OR (95% CI)
Proteinuria	7	10.1	5	13.2	1.3 (0.4–4.6)	3	13.6	1.4 (0.3–5.9)	13	43.3	6.8 (2.3–19.6)
Low GFR	16	23.2	10	26.3	1.2 (0.5–3.0)	6	27.3	1.2 (0.4–3.7)	19	63.3	5.7 (2.3–14.5)
Hypertension	7	10.1	4	10.5	1.0 (0.3–3.8)	1	4.5	0.4 (0.1–3.6)	10	33.3	4.4 (1.5–13.2)
Low GFR and proteinuria	1	1.4	2	5.3	3.8 (0.3–43.1)	2	9.1	6.8 (0.6–78.9)	8	26.7	24.7 (3.0–208.9)
Any long-term sequelae	25	36.2	15	39.5	1.2 (0.5–2.6)	8	36.4	1.0 (0.4–2.7)	26	88.7	11.4 (3.6–36.5)

Odds ratio (OR) and 95% confidence interval (95% CI) were calculated in comparison with patients with no oliguria
GFR glomerular filtration rate

also found to be an independent predictor of all renal-related sequelae ($p < 0.001$). These findings persisted when controlling for age at admission, gender, and length of follow-up in multivariate logistic regression models.

Among patients with anuria (Table 4), there was a stepwise increase in the incidence of all sequelae as the duration of anuria increased. This was most notable once anuria exceeded 5 days in duration, at which time the incidence of all sequelae, with the exception of hypertension, increased substantially. In one example, the incidence of at least one sequel in those with a history of 1–5 days of anuria rose from 42.1% to 68.2% if the anuria persisted for 6–10 days. The incidence of proteinuria likewise increased from 13.2% to 31.8%, low GFR from 26.3% to 50.0%, and the combination of proteinuria and low GFR from 7.9% to 44.4% (see Table 4 for ORs and 95% CIs). Increase in the incidence of low GFR and proteinuria in patients with >10 days of anuria was associated with an OR of 9.8 (95% CI 1.7–57.5); it rose to 57.8 (95% CI 141–544) after controlling for age at hospital admission, decade of treatment, gender, and length of follow-up.

Hypertension, the incidence of which was similar in those with a history of 1–5 days (15.8%) and 6–10 days (13.6%) of anuria, increased markedly to 55.6% if anuria persisted for >10 days. The adjusted ratio for hypertension in patients with >10 days of anuria was 13.1 (95% CI 2.8–60.7) when controlling for age at admission, decade of treatment, gender, and length of follow-up.

Results of multivariate logistic regression analysis

The most significant predictor of sequelae (anuria duration) was entered into the multivariate regression equation first and its effect controlled in comparison with other clinical variables from the acute phase of the illness. Variables from the acute phase included WBC, HCT, creatinine, and BUN at admission. After the effect of anuria was controlled for, none of the other variables achieved statistical significance. This finding may reflect the fact that the other variables have a high degree of correlation with one another. Similar results were seen when oliguria was entered into the equation first and its effect was controlled for.

Discussion

Although the majority of studies [2, 6, 9, 14–18], including our own [2, 10], conclude that oliguria and anuria duration are major prognostic indicators, there have been few attempts to specifically quantify this relationship. It should be noted that larger studies with longer periods of follow-up [9, 18, 19] are generally necessary to obtain statistically

Table 4 Relationship between anuria duration (in days) and the risk of long-term renal-related sequelae

Duration of anuria (days)	None		1–5 Days			6–10 Days			> 10 Days		
	80	%	38	%	OR (95% CI)	22	%	OR (95% CI)	9	%	OR (95% CI)
Proteinuria	10	11.1	5	13.2	1.2 (0.4–3.8)	7	31.8	3.7 (1.2–11.4)	6	66.7	16.0 (3.5–74.2)
Low GFR	23	25.6	10	26.3	1.0 (0.4–2.5)	11	50.0	2.9 (1.1–7.6)	7	77.8	10.2 (1.0–1.5)
Hypertension	8	8.9	6	15.8	1.9 (0.6–6.0)	3	13.6	1.6 (0.4–6.7)	5	55.6	12.8 (2.9–57.5)
Low GFR and proteinuria	2	2.2	3	7.9	3.7 (0.6–23.6)	4	18.2	9.8 (1.7–57.5)	4	44.4	35.2 (5.1–240.5)
Any long-term sequelae	34	37.8	16	42.1	1.2 (0.6–2.6)	15	68.2	3.5 (1.3–9.6)	9	100.0	-

Odds ratio (OR) and 95% confidence interval (95% CI) were calculated in comparison with patients with no anuria
GFR glomerular filtration rate

significant information. Studies with smaller numbers of patients [3, 16, 20] and/or shorter periods of follow-up have often resulted in conclusions markedly different from those with larger sample sizes. This study describes a relatively large number of patients (159) with a mean follow-up that is substantial for such a large cohort (8.75 years). Another long-term follow-up study, but with a markedly smaller sample size, illustrates the importance of long-term follow-up to determine the true prevalence of renal-related sequelae [3].

Anuria served as a better predictor for most chronic renal sequelae than did oliguria. Furthermore, longer duration of either oliguria (> 10 days) or anuria (> 5 days) correlated with higher incidence in all sequelae measured. Of particular importance were the dramatic increases seen in the prevalence of proteinuria, low GFR, and low GFR combined with proteinuria once anuria or oliguria exceeded 10 days in duration. Such a strongly correlated relationship provides evidence of a link between the severity of initial renal injury and eventual outcome.

It is noteworthy that a substantial number (approximately 36%) of children with no recorded oliguria or anuria were left with sequelae. Moreover, proteinuria, a recognized sign of hyperfiltration injury, is seen in about 10% of those with no recorded oliguria or anuria. Although these abnormalities have so far remained mild, there is concern about the adverse effects of pregnancy and normal glomerular obsolescence as these survivors move through adulthood.

The tabulated models presented here may serve as quantitative predictors of long-term renal-related sequelae and may help identify patients who, at the time of hospital discharge, require extended follow-up. The predictive value for long-term sequelae was particularly strong in individuals who experienced anuria. This general trend provides evidence of the predictive value of oliguria or anuria duration and is one of the few noninvasive quantitative predictors available.

Based on our collective experience, we suggest that all patients be evaluated yearly during the first decade following D+HUS then, if normal, every 2 years during the second decade, and if normal then, every 5 years for life. These evaluations should include a measurement of GFR, a calculation of albumin/creatinine ratio using a first morning urine specimen, and careful blood pressure measurements. Those with signs of hyperfiltration injury (microalbuminuria and/or overt proteinuria) need to be evaluated more often during pregnancies and as they progress through the midlife years, a time when normal glomerular obsolescence might further stress the remaining nephron population.

This admittedly is a cautious approach but one we feel is reasonable until we have had the opportunity to track a sizable cohort throughout their lives. Of major concern is the long-term outlook for those with chronic kidney disease, including reduced GFR and persistent proteinuria. This group is at high risk for eventual advancement through the stages of chronic kidney disease and therefore should be evaluated at more frequent intervals. Based on the findings of this study, patients with > 10 days of oliguria or > 5 days of anuria warrant more careful monitoring.

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References

1. Siegler RL (1995) The hemolytic uremic syndrome. Pediatr Clin North Am 42:1505–1529
2. Siegler RL, Milligan MK, Burningham TH, Christofferson RD, Chang SY, Jorde LB (1991) Long-term outcome and prognostic indicators in the hemolytic-uremic syndrome. J Pediatr 118:195–200
3. Gagnadoux MF, Habib R, Gubler MC, Bacri JL, Broyer M (1996) Long-term (15–25 years) outcome of childhood hemolytic-uremic syndrome. Clin Nephrol 46:39–41
4. Caletti MG, Gallo G, Gianantonio CA (1996) Development of focal segmental sclerosis and hyalinosis in hemolytic uremic syndrome. Pediatr Nephrol 10:687–692
5. Tonshoff B, Sammet A, Sanden I, Mehls O, Waldherr R, Scharer K (1994) Outcome and prognostic determinants in the hemolytic uremic syndrome of children. Nephron 68:63–70
6. Robson WL, Leung AK, Brant R (1993) Relationship of the recovery in the glomerular filtration rate to the duration of anuria in diarrhea-associated hemolytic uremic syndrome. Am J Nephrol 13:194–197
7. Blahova K, Janda J, Kreisinger J, Matejkova E, Sediva A (2002) Long-term follow-up of Czech children with D+hemolytic-uremic syndrome. Pediatr Nephrol 17:400–403
8. Hogg RJ, Portman RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J (2000) Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk, Assessment, Detection, and Elimination (PARADE). Pediatrics 105:1242–1249
9. Huseman D, Gellermann J, Vollmer I, Ohde I, Devaux S, Ehrich JH, Filler G (1999) Long-term prognosis of hemolytic uremic syndrome and effective renal plasma flow. Pediatr Nephrol 13:672–677
10. Siegler RL, Pavia AT, Christofferson RD, Milligan MK (1994) A 20-year population-based study of postdiarrheal hemolytic uremic syndrome in Utah. Pediatrics 94:35–40
11. Schwartz GJ, Haycock GB, Edelmann CM Jr., Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58:259–263
12. Goolsby MJ (2002) National Kidney Foundation Guidelines for chronic kidney disease: evaluation, classification, and stratification. J Am Acad Nurse Pract 14:238–242
13. Park HY, Schumock GT, Pickard AS, Akhras K (2003) A structured review of the relationship between microalbuminuria

and cardiovascular events in patients with diabetes mellitus and hypertension. Pharmacotherapy 23:1611–1616
14. Mizusawa Y, Pitcher LA, Burke JR, Falk MC, Mizushima W (1996) Survey of haemolytic-uraemic syndrome in Queensland 1979–1995. Med J Aust 165:188–191
15. Spizzirri FD, Rahman RC, Bibiloni N, Ruscasso JD, Amoreo OR (1997) Childhood hemolytic uremic syndrome in Argentina: long-term follow-up and prognostic features. Pediatr Nephrol 11:156–160
16. Mencia Bartolome S, Martinez de Azagra A, de Vicente Aymat A, Monleon Luque M, Casado Flores J (1999) Uremic hemolytic syndrome. Analysis of 43 cases. An Esp Pediatr 50:467–470
17. Arora P, Kher V, Gupta A, Kohli HS, Gulati S, Rai PK, Kumar P, Sharma RK (1994) Pattern of acute renal failure at a referral hospital. Indian Pediatr 31:1047–1053
18. Loirat C (2001) Post-diarrhea hemolytic-uremic syndrome: clinical aspects. Arch Pediatr 8(Suppl 4):776s–784s
19. Zurowska A, Gockowska Z, Czarniak P, Marczak E (2000) Changing clinical course of hemolytic uremic syndrome in children. Pol Merkuriusz Lek 8:234–235
20. Kelles A, Van Dyck M, Proesmans W (1994) Childhood haemolytic uraemic syndrome: long-term outcome and prognostic features. Eur J Pediatr 153:38–42