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Altered Renovascular Resistance After Spontaneous Recovery From Hemolytic Uremic Syndrome

Jennifer A. O'Brien, Scott K. Van Why[a], Marc S. Keller[a,b], Karen M. Gaudio[a], Thomas L. Kennedy[c], and Norman J. Siegel[a,d]

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[a]*Departments of Pediatrics and* [b]*Diagnostic Imaging*
Yale University School of Medicine and Yale-New Haven Hospital,
New Haven, Connecticut
Department of Pediatrics, Hospital of St. Raphael
New Haven, Connecticut,
and [c]*Department of Pediatrics, Bridgeport Hospital*
Bridgeport, Connecticut

Twenty-three patients were evaluated from 1-15 (mean 6) years after recovering from an episode of diarrhea-associated childhood hemolytic uremic syndrome (DA-HUS). All patients had received only conservative treatment; none had been given experimental, anti-coagulant, or immunological therapies. Follow-up studies included morphologic and duplex Doppler sonograms. Doppler sonography was used to determine the resistive index, a measure of renovascular resistance. Histories and physical examiniations revealed no abnormalities. Results of laboratory studies, which included calculated glomerular filtration rates, were all within normal limits, except for one patient with minor urinary abnormalities. Renal sonograms showed no significant abnormalities of kidney length or parenchymal appearance. However, Doppler sonographic examinations revealed that the DA-HUS patients demonstrated less of a decrease in renovascular resistance with age than did the control group ($p<0.0002$). After recovery, patients treated exclusively with conservative management during an acute episode of DA-HUS appeared to have an excellent long-term prognosis. Comparison of our results with those from other studies in which investigational therapies have been used during the acute phase of DA-HUS suggests that latent toxicities which cause long term sequelae may not have been appreciated previously. The clinical significance of the altered renal vascular resistance remains to be delineated.

INTRODUCTION

HUS[e] is defined by the acute onset of microangiopathic hemolytic anemia, thrombocytopenia, and renal dysfunction. DA-HUS is the most common form of the disease [1]. It usually follows a diarrheal prodrome and may be accompanied by central nervous system complications including seizures and coma [1, 2]. Over the past several decades, the recognition and diagnosis as well as true incidence of DA-HUS has increased, and this entity is currently considered to be the most common cause of acute renal failure in infants and children in developed countries [1, 3, 4]. The short-term outcome is generally excellent and appears to be fairly consistent among various institutions despite the use of varying modes of therapy [3-17]. However, less is known about the long term prognosis for patients who appear to recover completely from the acute episode.

[d]*To whom all correspondence should be addressed.* Department of Pediatrics, Yale University School of Medicine, New Haven, CT 06520
[e]*Abbreviations used:* HUS, hemolytic uremic syndrome; DA-HUS, diarrhea-associated hemolytic uremic syndrome; US, ultrasound; YNNH, Yale New-Haven Hospital; BUN, blood urea nitrogen, RI, resistive index, ESRD, end-stage renal disease; TMA, thrombotic microangiopathy.

This report describes the experience at Yale University School of Medicine where 23 children were treated for DA-HUS between 1974 and 1989. All patients studied had initially recovered spontaneously and completely from the acute episode of DA-HUS from 1-15 years previously and had received only conservative, supportive therapy. Renal duplex Doppler sonographic techniques, as well as standard laboratory and clinical measurements, allowed for a non-invasive assessment of renal status. Doppler sonograms were used to derive the resistive index (RI), a measure of renovascular resistance. The RIs of the study group were compared to those of a group of normal patients of similar ages. The goals of this study were a) to define the long term outcome for children who were treated conservatively for DA-HUS, and who appeared to have a complete recovery from the initial acute episode, b) to evaluate long-term complications which occur in this group of patients who were treated conservatively relative to other patients who received investigational therapies, and c) to determine if any residual changes in renal blood flow were present in these patients.

METHODS

This study was approved by the Human Investigations Committee of Yale University School of Medicine.

Patients. Computerized listings of the discharge diagnoses from the Pediatric Services of Yale-New Haven Hospital, the Hospital of St. Raphael (New Haven, CT), and Bridgeport Hospital (Bridgeport, CT) between January 1, 1974 and December 31, 1989, were reviewed to determine those patients with a diagnosis of hemolytic uremic syndrome. The following data were recorded from the medical records of these patients: demographic information and presenting symptoms; laboratory data on admission BUN, serum creatinine, hemoglobin, hematocrit, platelet count, and serum sodium, potassium bicarbonate, and chloride, and blood pressure on admission; maximum BUN, creatinine, and blood pressure values during the hospital stay; minimum hemoglobin, hematocrit, and platelet levels during hospitalization; the most abnormal urinalysis obtained during admission; the advent of oliguria (urine ouput $\leq$ 0.5 ml/kg/hr), length of oliguria, the need for dialysis, and length of dialysis, if performed; the need for transfusions and the type and amount of transfusions, if given; the occurrence of seizures, complications during the hospital stay, outcome, and length of hospital stay; and the results of the most recent follow-up evaluation available including blood pressure, urinalysis, BUN, serum creatinine, hemoglobin, hematocrit, platelet count, height, weight, and length of follow-up.

Patients who met the following criteria were eligible for this study: 1) Patients were less than 18 yr of age when diagnosed with hemolytic uremic syndrome, defined by the triad of microangiopathic hemolytic anemia (hematocrit < 30% and schistocytes on peripheral smear), thrombocytopenia (platelet count < 150,000/mm^3), and renal dysfunction (BUN > 18 mg/dl and a serum creatinine concentration > 1.2 mg/dl). 2) No evidence of recurrent or familial pattern of HUS. 3) Treatment with conservative, supportive management only, incuding dialysis and blood transfusions as necessary, but not with antithrombotic, antiplatelet, or fibrinolytic agents or with fresh frozen plasma, intravenous immunoglobulin, or plasmapheresis. 4) Apparent complete recovery from the acute illness as determined by hematocrit, platelet count, urine output, BUN, serum creatinine, and blood pressure. 5) Follow-up of one year or more after recovery from the acute episode.

Follow-up evalution. Subjects or their parents were mailed consent forms and letters explaining the project and were then contacted by telephone and asked to come to YNHH for follow-up studies. Follow-up evaluation included a medical history, physical examination, two blood pressure measurements always taken separately by the same two exam-

iners (J. O'B., S.V.W.) and measurements of height and weight. Blood was drawn and sent to the YNHH clinical laboratories for measurement of hemoglobin, hematocrit, platelet count, BUN, and serum creatinine concentrations. Analysis of fresh urine was performed using a dipstick (Labstix) to detect protein, glucose, ketones, or occult blood, and with examination of microscopic urine sediment by the same two observers (J. O'B., S.V.W.). Renal morphologic and duplex Doppler sonographic examinations were carried out by the same examiner (M.K.) who was unaware of patient's clinical status, using Mark 600 (Advanced Technology Laboratories, Bothell, WA) and Acuson 128 (Mountain View, CA) units.

The three patients who no longer lived in Connecticut were asked to submit the results of physical examinations, blood tests, and urinalyses performed by their private physicians. It was not possible to obtain renal sonograms of these subjects.

The following findings were considered abnormal: 1) systolic or diastolic blood pressures > 90th percentile for age and sex based on values of the Report of the Task Force on Blood Pressure Control in Children [18]; 2) heights or weights < 10th percentile for age and sex based on growth curves from the National Center for Health Statistics; 3) serum creatinine concentrations > 1.0 mg/dl; 4) glomerular filtration rates < 80 ml/min/1.73 m^2 as determined by the formula defined by Schwartz et al. [19]; 5) BUN concentrations > 20 mg/dl; 6) hemoglobin and hematocrit values less than standard values for age and sex [20]; 7) platelet counts < 150,000/mm^3; 8) urine protein levels > 30 mg/dL (1+ or greater detected by a dipstick); or 9) the presence of any casts, more than five leukocytes or more than five erythrocytes per high powered field in centrifuged urine sediment.

Sonographic examinations of renal morphology included determinations of kidney size, the presence or absence or renal scarring, abnormalities in the collecting system, such as calyceal or renal pelvic dilatation, and cortical-medullary differentiation. Kidney length was plotted against age, weight, height, and body surface area and compared to values for normal children [21]. Lengths above the 95th or below the 5th percentiles were considered abnormal. Doppler sonographic studies included determination of the resistive index at the level of the segmental renal arteries and examination for the presence of a patent main renal vein. The RI or Pourcelot index is defined as:

$$\frac{\text{[peak systolic velocity - end diastolic velocity]}}{\text{peak systolic velocity}}$$

The RI represents a quantitative assessment of the blood flow pattern through the vasculature and provides an assessment of renovascular resistance [22]. With increased resistance to flow, the RI increases because the wave form is more steep with increased systolic velocity and decreased diastolic velocity. This formula has been shown by Patriquin et al. to predict the severity of renal microangiopathy, vascular resistance, and the resolution of oliguria and anuria during the acute phase of hemolytic uremic syndrome [23]. These values were compared with those of a randomly chosen control group of 30 children (60 kidneys) of similar ages to the study subjects with no known renal or cardiac disease.

Statistical analysis. The acute phase variables of the subjects in the study group and of the patients lost to follow-up were compared using the Chi-square test with the Yates continuity correction, Fisher's exact test, or the two-tailed Student *t*-test, as appropriate, with a p value of $\leq .05$ considered significant. Comparison of the resistive indices of the DA-HUS group with those of the control group was done using a *z*-test. Relationships between continous variables were determined using the Pearson product-moment correla-

tion coefficient, linear regression analysis, the general linear model to determine P for each slope, and analysis of covariance. In all cases, $p \leq .05$ was considered significant.

RESULTS

Patient data. Forty-seven patients were initally identified as having been admitted with HUS to one of the three hospitals between January 1, 1974 and December 31, 1989. Overall, six (12.8%) of the 47 HUS patients never recovered normal renal function: four (8.5%) developed end-stage renal disease (ESRD) and two (4.3%) died during the acute phase. Of these six patients with poor acute outcome, three did not experience a diarrheal prodrome.

There were 41 patients with spontaneous recovery from the acute episode. One of these patients had experienced an episode of HUS associated with total body irradiation received in preparation for a bone marrow transplant and was not included in this study. One patient had a recurrence 15 mo after the initial episode. Of the remaining 39 patients with DA-HUS, 10 could not be located, but all had spontaneously recovered normal renal function by the time of discharge and maintained normal renal function for as long as they were followed (median follow-up period 1 mo., range 0 to 22 mo.). Twenty-three of the remaining 29 patients with DA-HUS agreed to participate in this study. The six patients who declined to participate were in good health with no known deterioration of renal function 1 to 16 yr. (median 4 yr.) after discharge.

Comparison of acute phase features of the patients in the study group with those of the sixteen patients lost to follow-up (10 not found and 6 refused to participate) revealed the following significant differences: oliguria was more frequent in the study group (68% *vs* 24%; $p < 0.02$), and peritoneal dialysis was required more often in the study group (55.5% *vs* 18%; $p < .05$). These differences suggest that the subjects in the study group may have actually experienced more severe episodes of HUS than did those lost to follow-up.

There were 15 females and 8 males in the final study group. All subjects were Caucasian, all had experienced DA-HUS and the mean age of admission to the hospital during the acute illness was 4.1 ± 2.8 yr. (median - 3.5 yr.; range - 6 weeks to 12 yr.). Laboratory values upon admission to the hospital showed that renal function studies, hematocrit, and platelet count were already markedly abnormal. The admission electrolyte values were generally within normal limits except for bicarbonate values which were low. Blood pressure was within normal limits for all patients.

Laboratory values, which define HUS, demonstrated progression of the illness after admission, with overall worsening of renal function (median BUN rose from 71 to 100 mg/dl; median creatinine rose from 2.8 to 3.9 mg/dl), anemia (median hemoglobin fell from 7.7 to 6.1 g/dl; median hematocrit fell from 22.9 to 17.9%), and thrombocytopenia (median platelet count fell from 67,000/mm^3 to 45,000/mm^3). Median systolic and diastolic blood pressures also rose by 29 and 14 mm Hg, respectively. Thus, patients were admitted to the hospital with laboratory values which were compatible with a diagnosis of HUS and their disease reached a peak during the hospital stay.

Fifteen patients (68%) were oliguric and twelve (55%) subsequently required peritoneal dialysis. These patients were dialyzed for an average of 9 ± 6 d. (median 7.5 d., range 2 ± 21 d.). Ten patients (45%) received blood transfusions. No patients received platelet transfusions. Five patients (23%) experienced seizures. The mean length of hospital stay was 13 ± 9 d. with a range from 3 to 33 d. (median 11 d.). There was no relationship between any of the acute phase variables (*see* Methods) and final outcome.

Follow-up Data (Table 1). The mean length of follow-up was 6 yr. with a range from 1 to 15 years. All 23 patients had reportedly been in good health since recovering from their

Table 1. Follow-up data.

Pt. #	Age (yrs)	Sex	F/U (yrs)	BP (mmHg)	U/A	BUN (mg/dl)	Cr (mg/dl)	GFR (cc/min/1.73m^2)	Hct (%)	Hb (g/dl)	Platelets (x1000)
1	7	F	1.8	88/58	nl	12	0.6	111.1	38.8	12.8	240
2	5	F	1.8	104/64	nl	13	0.4	137.5	[a]33.6	11.4	227
3	15	F	12.8	104/70	nl	12	0.9	101.1	[a]36.8	12.4	272
4	21	F	8.8	130/80	nl	13	0.8	108.5	37.1	12.1	219
5	4	F	1.5	102/58	nl	6	0.5	126.3	37.2	12.2	398
6	13	M	12.7	106/64	nl	19	0.7	149.5	41.5	13.7	350
7	11	M	9.2	92/56	nl	17	0.6	130.4	41.6	13.7	226
8	5	F	1.0	84/56	nl	17	0.7	82.5	36.5	11.7	290
9	6	M	1.0	90/60	nl	9	0.4	164.2	36.4	12.6	301
10	7	F	3.2	90/56	nl	15	0.5	142.0	38.9	13.1	415
11	10	M	7.25	92/60	nl	16	0.6	118.5	42.5	13.9	318
12	15	F	9.1	112/66	nl	11	0.7	124.6	38.6	13.0	306
13	12	F	8.2	92/60	nl	13	0.5	160.9			
14	12	F	9.3	108/64	nl	16	0.6	128.8	41.4	13.9	324
15	12	F	7.2	100/58	nl	11	0.8	101.3	36.7	12.9	253
16	14	M	11.7	114/72	nl	13	0.7	183.8	38.8	12.9	179
17	7	F	3.3	90/58	nl	15	0.6	120.4	[a]33.1	11.2	316
18	13	F	6.8	90/70	nl	18	0.7	126.5	35.7	12.0	320
19	22	M	15.3	120/80	nl	10	1.1	110.5	44.4	15.6	270
20	5	F	1.4	96/70	nl	19	0.4	140.9	35.6	12.2	383
21	3	F	1.4	106/75	1+pr	32	0.5	98.8	35.6	12.2	383
22	5	M	1.0	82/54	nl	17	0.4	139.2	37.8	12.3	458
23	13	M	1.5	86/60	nl	14	0.6	137.3	35.9	12.8	220
Mean(SD)	10(5)		6.0(4.6)	99(12)/64(8)		15(5)	0.6(0.2)	128.0(23.5)	37.9(2.9)	12.8(1.0)	307(73)
Median	11		6.8	96/60		14	0.6	126.5	37.2	12.7	304
Range	3-22		1.0-15.3	82-130		6-32	0.4-1.1	82.5-183.8	33.1-44.4	11.2-15.6	179-458

F/U=length of follow-up; BP=blood pressure; s=systolic; d=diastolic; U/A=urinalysis; Cr=serum creatinine; Hct-hematocrit; Hb=hemoglobin

[a]Hematocrit within 1% of lower limit of normal; [b]Elevated BUN & Upr:Ucr = 0.53

acute episode of DA-HUS.

All patients were at or above the 10th percentile for height and weight for their age and sex. All patients (from whom previous height and weight data were available) had maintained their appropriate growth curves. No systolic or diastolic blood pressures were above the 80th percentile for age and sex. All patients had normal physical examinations including fundoscopic, heart, lung, abdominal, extremity, and neurologic examinations.

All hematological data were normal except for 3 hematocrit values within 1% of the lower limit of normal. Urinalysis and renal function studies were normal in 22 of 23 patients (Table 1): mean serum creatinine concentration was 0.6 ± 0.2 mg/dl (range 0.4 - 1.1 mg/dl); BUN, 15 ± 5 mg/dl (range 6 - 32 mg/dl); and creatinine clearance, (128.0 ± 23.5 ml/min/1.73m^2). One patient (#21) had an abnormal urinalysis (1+ protein and a single granular cast), an elevated urine protein: creatinine ratio of 0.53 (normal < .20), and a BUN of 32 mg/dl. Her calculated GFR was 98.8 mL/min/1.73m^2.

Ultrasound Data (Table 2). Evaluation of 40 kidneys from 20 subjects (patients #15, #16, and #23 were not available to study) using renal sonography to measure longitudinal kidney length showed no kidneys to be smaller than the 5th percentiles for age, height, or weight. The length of the left kidney of subject #10 was at the 95th percentile for weight only. The length of the left kidney of patient #12 was greater than the 95th percentile for height only. The length of the right kidney of patient #17 was greater than the 95th percentile for age, height, and weight. In each case (#10, #12, #17), the contralateral kidney was within 1 cm of the larger kidney; thus, the increased size of the larger kidney was not

Table 2. Longitudinal kidney lengths measured by sonography.

1	7	F	121.2	24	8.1	8.3
2	5	F	100.0	17	7.1	7.1
3	15	F	165.4	54	10.0	11.0
4	21	F	157.8	69	12.2	12.1
6	13	M	114.8	22	7.6	7.9
7	11	M	142.2	37	8.9	9.2
8	5	F	105.0	18	8.5	8.5
9	6	M	119.4	22	8.2	8.9
10	7	F	129.1	21	7.9	[a]8.9
11	10	M	129.3	31	9.0	8.2
12	15	F	158.6	56	10.6	[b]11.5
13	12	F	146.0	39	9.4	10.3
14	12	F	140.0	33	9.1	9.3
17	7	F	131.0	31	[c]10.1	9.0
18	13	F	161.0	40	10.3	10.7
19	22	M	173.6	87	11.0	11.6
20	5	F	102.5	17	7.7	7.2
21	3	F	89.7	14	6.8	7.2
22	5	M	101.2	17	7.2	7.6
Mean	10(5)				8.9(1.4)	9.2(1.5)
Median	8.5				9.0	9.1
Range	3-22				6.8-12.2	7.1-12.1

R.K. = Right Kidney; L.K. = left kidney

[a]Length = 95th percentile for weight only

[b]Length = 95 percentile for height only

compensatory growth because of a small opposite kidney. There were no signs of renal scarring, collecting system abnormalities, or abnormal cortical-medullary differentiation seen on any of the sonograms. There were no scarred, shrunken or small kidneys.

Doppler sonography was used to derive RIs of the vascular flow pattern and to compare the renovascular resistance in the DA-HUS subjects (40 post-HUS kidneys) to those of 30 randomly selected control subjects (60 normal kidneys). At the time of Doppler examination, median age of DA-HUS was 8.1 yr. (range 3-22 yr.) and median age of control group was 8.2 yr. (range 0-16 yr.). The mean RIs of the DA-HUS and control groups were not significantly different (.66 ± .05 and .67 ± .07, respectively). Both groups showed a statistically significant decrease in RI with increasing age (DA-HUS: $r^2 = .121$, $p = .0277$; control: $r^2 = .492$, $p < .0001$; Figure 1). However, using covariance analysis, the DA-HUS patients demonstrated less of a decrease in RI with age than did the control group ($p < .0002$). Thus, for the DA-HUS patients, RI values overall were higher than expected for a given age. The RIs of these patients were not studied longitudinally, the patients had their acute illness at different ages and have had various lengths of follow-up. Therefore, it is difficult to determine for certain the trend of individual RIs over time and whether the rate of RI decrease slowed, stopped falling completely, or even began to rise after the initial episode of DA-HUS. However, in the DA-HUS patients, age correlated with length of time since hospitalization ($r^2 = .78$, $p < .0001$). Furthermore, when RI was compared to length of follow-up, RI was found to fall slightly but significantly as length of time since the acute illness increased ($r^2 = .248$, $p = .0011$; Figure 2). Taken together, these data suggest that renal vascular resistance in this group of children who recovered from DA-HUS was decreasing over time as it does in normal children, although at a significantly slower rate than was observed in the control group.

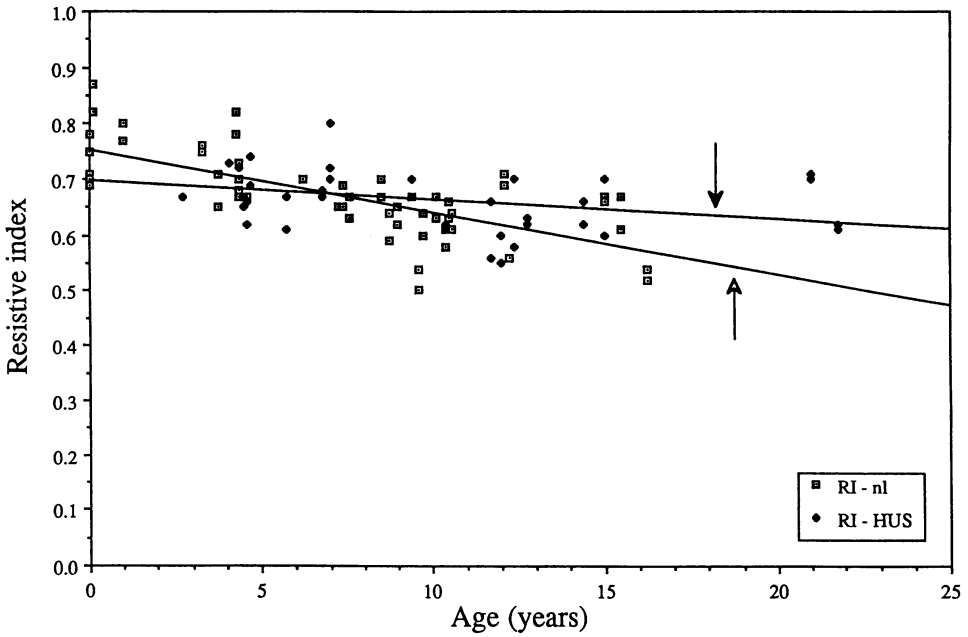

Figure 1. Correlations between resistive indices and age of 20 HUS subjects and 30 controls. Closed arrow - HUS (n = 40 kidneys): $y = .70-.003x$, $r^2 = .121$, $p = 0.0277$; open arrow - control (n = 60 kidneys): $y = .75-.011x$, $r^2 = .492$, $p < .0001$

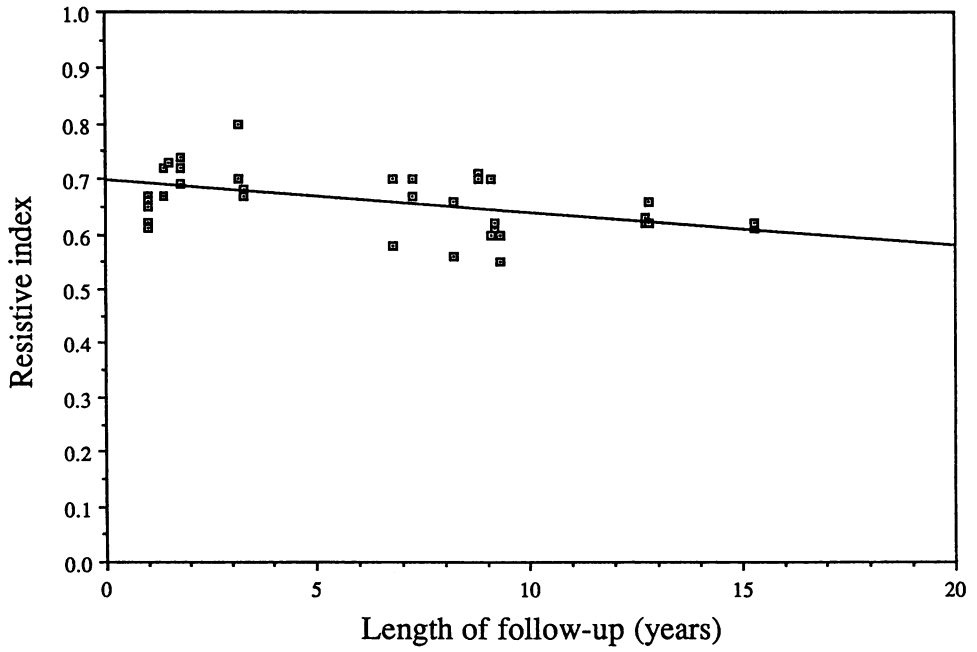

Figure 2. Correlation between resistive indices and length of follow-up in 20 HUS patients (n = 40 kidneys): y = 0.70-0.006x, r^2 = .248, p =.0011.

DISCUSSION

There have been many reports which describe the immediate outcome of childhood DA-HUS (Table 3). Overall, acute mortality has improved dramatically over the past 20 yr. This has been attributed, in part, to increasing recognition of milder cases of HUS as well as to improved supportive management. Gianantonio, who has reported the largest number of HUS patients, noted that over 15 years the acute mortality rate dropped from 47% to 6.25% with increasing use of peritoneal dialysis [2]. The question of whether or not to pursue more aggressive therapy has been controversial.

Damage to endothelial cells caused by an *E.coli* 0157:H7 Vero cell cytotoxin (VT1 or SLT-I) is currently considered the primary pathogenic mechanism of classic HUS [1, 30-33]. The fibrin depositions associated with TMA have led investigators to suggest additional mechanisms including activation of intravascular coagulation cascade, platelet activation, and prostacyclin deficiency [2, 34, 35]. Therefore, therapeutic interventions with anti-thrombotic agents such as anti-coagulants, platelet inhibiting agents, and fibrinolytic agents to minimize the extent and effects of TMA have been tried [6, 27, 36, 37]. There have also been trials of plasmapheresis and infusions of fresh frozen plasma, prostacyclin, and immunoglobulin attempting to correct the proposed deficiencies in prostacyclin synthesis and other abnormal factors found in the sera of HUS patients [14, 15, 38-40]. None of these therapies has been shown to improve definitively or significantly the acute outcome of DA-HUS.

Table 3. Data on short-term outcome of infants and children with HUS: Review of literature.

Author[ref]	Location	No. of pts.	Therapy(#)	Died(%)	ESRD&	Recovered(%)
Kaplan et al.	Johannesburg,	67	heparin(8)	34.3	---	---
1971[24]	South Africa	39(lit.rev.)	heparin	33.0		
Gianantonio	Buenos Aires	678	heparin(26)	11.0	---	---
et al.1973[2]						
Vitacco et al.	Buenos Aires	10	heparin	40	---	---
1973[25]		20	none	30		
Powell et al.	Melbourne,	14	heparin	36	29	36
1974[26]	Australia	22	none	41	23	36
		8	multiple	25	0	75
Proesmans	Leuven,	191	heparin	16.8	---	---
et al.1974[27]	Belgium	1012	none	20.6		
van Wieringen	Netherlands	212	?	16	---	---
et al. 1974[28]						
Janssen et al.	Brussels	20	heparin(1)	15	10	75
1974[29]						
Kaplan et al.	Johannesburg,	44	none	4.5	---	---
1976[5]	South Africa					
Monnens et al.	Netherlands	35	heparin	5.7	---	---
1978[6]		38	streptokinase	7.9	---	---
Sorrenti et al.	Chicago	4	heparin	25	---	---
1978[7]	(IL & IN)	15	none	0		
Dolislager et al.	Stanford, CA	45	none	2	9	89
1978[8]						
Donckerwolcke	Utrecht	72	?	17	12.5	71
et al. 1979[9]						
Binda Ki Muaka	Leuven,	45	heparin	6.6	4.4	86.7
et al.1981[10]	Belgium					
Habib et al.	Paris	70	heparin(45)	7	15.7	77
1982[11]						
Trompeter et al.	London	72	variable	4	23.6	69.4
1983[12]						
Loirat et al.	Paris	67	variable	7	---	---
1984[13]						
Loirat et al.	Paris	39	FFP	5	5	90
1988[14]		40	none	5	5	90
Rizzoini et al.	Italy	17	FFP	0	0	100
1988[15]		15	none	0	0	100
van Dyke et al.	Leuven,	54	?	5.6	5.6	89
1988[16]	Belgium					
Tarr et al.	King County,	59	?	3.4	---	---
1989[3]	Washington					
Martin et al.	Minnesota	117	?	3.4	14	82
1990[4]						
Siegler et al.	Salt Lake City,	118	?	2.5	---	---
1991[17]	Utah					

Overall mortality (4.3%) and morbidity (8.5% ESRD) rates for the present series during the acute stage of the illness are comparable to those previously reported (Table 3). The mortality and morbidity of the present series of patients with DA-HUS who were managed conservatively are compatible with other series which include experimental therapeutic interventions. Moreover, since an entry criterion of this study was an apparent spontaneous resolution of the acute episode of DA-HUS, it is important to note that follow-up data are not biased by high acute morbidity or mortality.

Published observations of long term follow-up status of children with HUS are highly variable (Tables 3 and 4). Over the past 20 yr., long-term follow-up studies have shown the proportion of patients without any sequelae to range from 60-97% (excluding the particularly severe cases reported from Argentina). Proportions of patients with residual hypertension (0-20%), proteinuria (0-32%), low creatinine clearances (0-57%), and chronic renal failure (0-11%) have also been inconsistent. Interpretation of these large variations in outcome is difficult. Most long-term follow-up studies describe collectively all HUS patients, some or all of whom were often acutely treated with multiple and differing therapeutic approaches and some of whom did not have a diarrheal prodrome. Occasionally, there is no mention of how patients were treated during the acute episode. The putative effects of experimental therapies, administered during the acute episode, on long-term outcome are not known. Various experimental interventions could have had significant effects on later outcome that were not, initially, appreciated or anticipated. Many long-term follow-up studies also do not distinguish a recovery group from those who never regained renal function when reporting rates of long term sequelae.

Another issue confounding the data on later sequelae of childhood HUS is the difficulty of detecting early renal insufficiency non-invasively. Standard measurements of renal function (serum creatinine and BUN) may not become detectably abnormal until renal failure is fairly advanced. O'Regan et al. found no correlation between abnormal GFR measured by ^{99m}TcDTPA plasma slope clearance and normal BUN and plasma creatinine concentrations in follow-up of patients with HUS [41] which raises the possibility that some post-HUS patients with residual chronic renal insufficiency are being missed.

This follow-up study of HUS patients differs from many previous similar studies in that all subjects had DA-HUS and were treated conservatively during the acute illness. Thus, the problem of various, confounding acute therapies which might complicate the natural history of recovery from HUS is eliminated. Also, this follow-up study focussed exclusively on those patients who recovered completely from the initial episode. Finally, in addition to routine follow-up testing, this study incorporated measurements of creatinine clearance as well as sonographically determined kidney size, appearance, and renovascular resistance as indications of residual renal injury.

Comparison of features during the acute phase indicated that those lost to follow-up (16 of 39 eligible patients) may have experienced a less severe course than did those in the study. This suggested that the observed outcomes in the study group were not biased because of a mild initial phase of HUS. Thus, it seems unlikely that the parameters examined underestimated the rates of later sequelae for the entire group.

Calculated GFRs which are based on serum creatinine concentrations may overestimated true renal function [41, 42]. Thus, subtle decreases in GFR may have been undetected. However, the outcome measures used in this study were those most commonly available, and the estimation of GFR by the Schwartz formula has been shown to correlate closely with inulin clearance [19]. If substantial declines in GFR were present, one would have anticipated that abnormalities in kidney size, composition, or shape would also have been present and these latter alterations were not detected.

By routine criteria, including GFR calculations, none of the patients in this study

Table4. Data on longterm follow-up of children with HUS: Review of the literature

Author [ref]	Location	No. of patients followed	Length of follow up (years)	Therapy during acute phase (#)	No. of pts. normal at f/u	Sequelae: CRF	HTN	Proteinuria	Creatinine clearance <80ml/m/1.73m^2
Gianantonia et al. 1973 [2]	Buenos Aires	124	5-13	Heparin (26)	50(40%)	10(8%)	18(15%)	40(32%)	51(41%)
Janssen et al. 1974 [29]	Brussels, Belgium	17	.25-12	None	15(90%)	0	1(5%)	2(10%)	---
Kaplan et al. 1976 [5]	South Africa	33	0.5-6	None	30(91%)	1(3%)	3(9%)	1(3%)	---
Dolislager et al. 1978 [8]	California	42	1-12	None	38(90%)	4(10%)	4(10%)	5(12%)	4(10%)
Monnens et al. 1978 [6]	Rotterdam-Nijmegen, The Netherlands	68	2	Heparin& streptokin	?	0	5(7%)	10(14%)	4(6%)
Sorrenti et al. 1978 [7]	Chicago, IL	16	1.5-8	Heparin(3)	14(88%)	0	1(6%)	1(6%)	0
Binda kiMuaka et al. 1981 [10]	Leuven, Belgium	39	3-8	Heparin	38(97%)	0	0	0	1(3%)
Loirat et al. 1984 [13]	Paris	56	1-7.6	Heparin, FFP fibrinolytics	37(60%)	6(11%)	11(20%)	?	14(25%)
Van Dyck et al. 1988 [16]	Belgium	46	10	?Heparin	32(70%)	2(4%)	4(8%)	5(11%)	3(7%)
O'Regan et al. 1989 [41]	Canada	37	6-11	?	0	0	0	7(19%)	21(57%)
Siegler et al. 1991 [17]	Utah	61	5-18	?	37(61%)	---	3(5%)	18(30%)	9(15%)
Fitzpatrick et al. 1991 [11]	U.K.	88	5-21	?	45(51%)	5(6%)	3(3%)	27(31%)	16(18%)

CRF: Chronic Renal Failure
HTN: Hypertension
FFP: Fresh Frozen Plasma

demonstrated any significant sequelae, thus appearing to exhibit more favorable outcomes than have patients reported elsewhere [2, 11, 13, 16, 17]. One patient had minor urine abnormalities noted on one examination. Furthermore, all kidneys measured were of normal size, and no evidence of renal parenchymal scarring was seen by sonographic evaluation. These results are most similar to those reported by Janssen [29], Kaplan [5], and Dolislager [8], who described a combined total of 92 HUS patients from Belgium, South Africa, and California, respectively. All of these patients were treated conservatively during the acute episode, and in each group 90% were without any sequelae at follow-up.

Other follow-up series have shown less successful outcomes (Table 4). Of note, the poorer outcome has been reported more frequently in studies in which experimental therapy was used during the acute episode or therapeutic intervention is not delineated. While it could be argued that more severely ill patients are selected for experimental therapies, the acute phase variables assessed in this study suggest that the incidence of oliguria, dialysis therapy, or seizures in our group of patients were similar to those reported by others. Thus, the poorer outcome reported in other studies is not necessarily from inclusion of patients who were more acutely ill compared to those reported in this study. Alternatively, it is possible that higher rates of sequelae seen in other studies resulted from latent side effects of various investigational therapies used during the acute episode. For example, Binda Ki Muaka et al. initially found complete recovery in 38 of 39 patients who had been treated with heparin and dipyridamole during the acute episode [10]. However, a re-evaluation of this same group of patients, by Van Dyck et al., found only 70% normal at 10 yr. follow-up [16]. Similarly, in a 5 - 21 yr. follow-up of 103 children with DA-HUS, Fitzpatrick et al. reported that 31% had microalbuminuria, 18% had reduced GFR, and 10% had both in association with higher systolic blood pressure [11]. Unfortunately, therapeutic interventions, during the acute phase of the illness, are not delineated in this latter study [11]. While our findings are not definitive, an intense and thorough evaluation of this possibility should be undertaken in those centers which have employed investigational therapies.

The only abnormality found among the patients in the present series was a significantly slower age-related decrease in renovascular resistance determined by Doppler ultrasound examination of the segmental renal arteries. This statistically significant difference in resistive index between DA-HUS and normal subjects did not appear to represent a clinically relevant difference, at least for up to 15 yr. after the acute episode. The increase in renal vascular resistance and diminished rate of decline in RI in HUS patients may reflect the irreversible injury to some glomeruli or microvascular beds during the acute episode. Whether or not the DA-HUS patients will eventually achieve normal RI values is unclear from the present data. Longer follow-up would be necessary to determine whether the RIs of these DA-HUS patients continue to fall until they reach normal levels, or whether after a certain age renal vascular resistance will plateau at a higher level and represent a harbinger of later sequelae, possibly in adulthood. This possibility would be compatible both with the poorer outcome reported by Fitzpatrick [11], whose patients were studied later in follow-up than ours, and with the observation by Siegler et al. that abnormalities appeared in some cases after an interval of apparent recovery [17].

In conclusion, this study indicates that patients who have recovered from DA-HUS with only conservative management have an excellent prognosis and provides supportive evidence for the efficacy and safety of conservative management of the acute phase of DA-HUS. However, the clinical implications of increased renovascular resistance, without other clinical sequelae, remain to be determined.

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1. Levin, M., Walters, M. D. S., and Barratt T. M. Hemolytic uremic syndrome. Adv. Pediatr. Infect. Dis. 4:51-82, 1989.
2. Gianantonio, C. A., Vitacco, M., Mendilaharzu, F., Gallo, G. E., and Sojo, E. T. The hemolytic-uremic syndrome. Nephron 11:174-192, 1973.
3. Tarr, P. I., Neill, M. A., Allen, J., Siccardi, C. J., Watkins, S. L., and Hickman, R. O. The increasing incidence of the hemolytic-uremic syndrome in King County, Washington: Lack of evidence for ascertainment bias. Am. J. Epidemiol. 129:582-586, 1989.
4. Martin, D. L., MacDonald, D. L., White, K. E., Soler, J. T., and Osterholm, M. T. The epidemiology and clinical aspects of the hemolytic uremic syndrome in Minnesota. N. Engl. J. Med. 323:1161-1167, 1990.
5. Kaplan, B. S., Thomson, P. D., and Chadrevian, J. P. The hemolytic uremic syndrome. Pediatr. Clin. N. America 23:761-777, 1976.
6. Monnens, L., van Collenburg, J., de Jong, M., Zoethout, H., and van Wieringen, P. Treatment of the hemolytic-uremic syndrome: Comparison of the results of heparin treatment with the results of steptokinase treatment. Helv. Paediat. Acta. 33:321-328, 1978.
7. Sorrenti, L.,Y. and Lewy, P. R. The hemolytic-uremic syndrome: Experience at a center in the Midwest. Am. J. Dis. Child. 132:59-62, 1978.
8. Dolislager, D. and Tune, B. The hemolytic-uremic syndrome: Spectrum of severity and significance of prodrome. Am. J. Dis. Child. 132:55-58, 1978.
9. Donckerwolcke, R. A., Kuyten, R. H., Tiddens, H. A., and Van Gool, J. D. Haemolytic uraemic syndrome. Paediatrician 8:378-393, 1979.
10. Binda, K. I., Muaka, P., Proesmans, W., and Eeckels, R. The haemolytic uraemic syndrome in childhood: A study of the long-term prognosis. Eur. J. Pediatr. 136:237-243, 1981.
11. Fitzpatrick, M. M., Shah, V., Trompeter, R. S., Dillon, M. J., and Barratt, T. M. Long term renal outcome of childhood haemolytic uraemic syndrome. Br. Med. J. 303:489-492, 1991.
12. Trompeter, R. S., Schwartz, R., Chantler, C., Dillon, M. J., Haycock, G. B., Kay, R., and Barratt, T.M. Haemolytic-uraemic syndrome: An analysis of prognostic features. Arch. Dis. Child. 58:101-105, 1983.
13. Loirat, C., Sonsino, E., Moreno, A. V., Pillion, G., Mercier, J. C., Beaufils, F., and Mathieu, H. Hemolytic-uremic syndrome: An analysis of the natural history and prognostic features. Acta. Paediatr. Scand. 73:505-514, 1984.
14. Loirat, C., Sonsino, E., Hinglais, N., Jais, J. P., Landais, P., and Fermanian, J. Treatment of the childhood haemolytic uraemic syndrome with plasma. Pediatr. Nephrol. 2:279-285, 1988.
15. Rizzoni, G., Claris-Appiani, A., Edefonti, A., Facchin, P., Franchini, F., Gusmano, R., Imbasciati, E., Pavanello, L., Perfumo, F., and Remussi, G. Plasma infusion for hemolytic-uremic syndrome in children: Results of a multicenter controlled trial. J. Pediatr. 112:284-290, 1988.
16. Van Dyck, M., Proesmans, W., and Depraetere, M. Hemolytic uremic syndrome in childhood: Renal function ten years later. Clin. Nephrol. 29:109-112, 1988.
17. Siegler, R. L., Milligan, M. K., Burningham, T. H., Christofferson, R. D., Chang, S-Y., and Jorder, L. B. Long-term outcome and prognostic indicators in the hemolytic-uremic syndrome. J. Pediatr. 118:195-200, 1991.
18. National Heart, Lung, and Blood Institute: Report of the Second Task Force on Blood Pressure Control in Children. Pediatr. (Suppl.) 79:1, 1987.
19. Schwartz, G. J., Haycock, G. B., Edelmann, C. M. Jr., and Spitzer, A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatr. 58:259-263, 1976.
20. Greene, M. G., ed. The Harriet Lane Handbook, 12th ed. Mosby Year Book, St. Louis, p. 42, 1991.
21. Han, B. K. and Babcock, D. S. Sonographic measurements and appearance of normal kidneys in children. A. J. R. 145:611-616, 1985.
22. Keller, M. S. Renal doppler sonography in infants and children. Radiol. 172:603-604, 1989.
23. Patriquin, H. B., O'Regan, S., Robitaille, P., and Paltiel, H. Hemolytic-uremic syndrome: Intrarenal arterial Doppler patterns as a useful guide to therapy. Radiol. 172:625-628, 1989.
24. Kaplan, B. S., Katz, J., Krawitz, S. and Lurie, A. An analysis of the results of therapy in 67 cas-

es of the hemolytic-uremic syndrome. J. Pediatr. 78:420-425, 1971.
25. Vitacco, M., Avalos, J. S., and Gianantonio, C. A. Heparin therapy in the hemolytic-uremic syndrome. J. Pediatr. 83:271-275, 1973.
26. Powell, H. R. and Ekert, H. Streptokinase and anti-thrombotic therapy in the hemolytic-uremic syndrome. J. Pediatr. 84:345-349, 1974.
27. Proesmans, W. and Eeckels, R. Has heparin changed the prognosis of the hemolytic-uremic syndrome? Clin. Nephrol. 2:169-173, 1974.
28. Van Wieringen, P. M. V., Monnens, L. A. H., and Schretlen, E. D. A. M. Haemolytic-uraemic syndrome: Epidemiological and clinical study. Arch. Dis. Child. 49:432-437, 1974.
29. Janssen, F., Potvliege, P. R., and Vainsel, M. Le pronostic a court et a long terme du syndrome hemolytique et uremique. Arch. Franc. Ped. 31:59-69, 1974.
30. Karmali, M. A., Petric, M., Lim, C., Fleming, P. C., Arbus, G. S., and Loir, H. The association between idiopathic hemolytic uremic syndrome and infection by verotoxin-producing Escherichia coli. J. Infect. Dis. 151:775-782, 1985.
31. O'Brien, A. D. and Holmes, R. K. Shiga and Shiga-like toxins. Microbiological Reviews 51:206-220, 1987.
32. Obrig, T. G., Del Vecchio, P. J., Karmali, M. A., Petric, M., Moran, T.P. and Judge, T.K. Pathogenesis of haemolytic uraemic syndrome. Lancet 2:687, 1987.
33. Kavi, J., Chant, I., Maris, M., and Rose, P. E. Cytopathic effect of verotoxin on endothelial cells. Lancet II: 1035, 1987.
34. Arenson, E. B. Jr and August, C. S. Preliminary report: Treatment of the hemolytic uremic syndrome with aspirin and dipyridamole. J. Pediatr. 86:957-961, 1975.
35. Webster, J., Rees, A. J., Lewis, P. J., and Hensby, C. N. Prostacyclin deficiency in haemolytic-uraemic syndrome. Br. Med. J. 281:271, 1980.
36. O'Regan, S., Chesney, R. W., Mongeau, J. G. and Robitaille, P. Aspirin and dipyridamole therapy in the hemolytic-uremic syndrome. J. Pediatr. 97:473-476, 1980.
37. Stuart, J., Winterborn M. H., White, R. H. R. and Flinn, R. M. Thrombolytic therapy in haemolytic-uraemic syndrome. Br. Med. J. 3:217-221, 1974.
38. Defreyn, G., Proesmans, W., Machin, S. .J ., Lemmens, F., and Vermylen, J. Abnormal prostacyclin metabolism in the hemolytic uremic syndrome: equivocal effect of prostacyclin infusions. Clin. Nephrol. 18:43-39, 1982.
39. Beattie, T. J., Murphy, A. V., Willoughby, M. L. N., Machin, S. J., and Defreyn, G. Plasmapheresis in the haemolytic-uraemic syndrome in children. Br. Med. J. 282:1667-1668, 1981.
40. Robson, W. L. M., Fick, G. H., Jadavji, T. and Leung, A. K. C. The use of intravenous gammaglobulin in the treatment of typical hemolytic uremic syndrome. Pediatr. Nephrol. 5:289-292, 1991.
41. O'Regan, S., Blais, N., Russo, P., Pison, C. F. and Rousseau, E. Hemolytic uremic syndrome: Glomerular filtration rate, 6 to 11 years later measured by 99mTcDTPA plasma slope clearance. Clin. Nephrol. 32:217-220, 1989.
42. Chandhoke, P. S., Kogan, B. A., Al-Dahwi, A., DuBois, J., and Holiday, M. A. Monitoring renal function in children with urological abnormalities. J. Urol. 144:601-605, 1990.