Pediatr Nephrol (1999) 13:672–677

ORIGINAL ARTICLE

**Dieter Hüseman · Jutta Gellermann · Ilka Vollmer
Iris Ohde · Siegmar Devaux · Jochen H.H. Ehrich
Guido Filler**

Long-term prognosis of hemolytic uremic syndrome and effective renal plasma flow

Received: 17 September 1998 / Revised: 31 March 1999 / Accepted: 1 April 1999

Abstract The long-term prognosis of diarrhea-associated hemolytic uremic syndrome (D+ HUS) was evaluated in a cohort of 127 of 149 children who had survived the acute phase. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were estimated by serial ^{51}Cr-EDTA and ^{123}iodine-hippurate clearances. All children had acute renal failure during the initial phase and 74% of patients were dialyzed. During the 1st year, mean GFR and ERPF increased continuously until a plateau was reached. In the 2nd year after the diagnosis of HUS, GFR was below 80 and ERPF below 515 ml/min per 1.73 m^2 in 16% and 47% of patients, respectively. At the end of a median follow-up of 5.0 (range 2.0–13.2) years, the proportion of children with renal sequelae such as proteinuria ≥300 mg/l, hypertension, or a GFR <80 ml/min per 1.73 m^2 was 23%. Anuria of more than 7 days' duration and hypertension during the acute phase were statistically significant risk factors for an unfavorable outcome. A reduced ERPF in the 2nd year was found in 93% of patients with sequelae. Mean filtration fraction (SD) in these patients was 0.26 (±0.07) versus 0.19 (±0.05) in patients without sequelae (P<0.0001). These data suggest that loss of nephrons during the acute phase may implicate hyperfiltration in the residual functioning kidney mass leading to progressive renal disease. ERPF in the 2nd year after D+ HUS may serve as an excellent parameter to detect patients with a high risk of an unfavorable long-term outcome.

Key words Hemolytic uremic syndrome · Effective renal plasma flow · Glomerular filtration rate · Hyperfiltration · Long-term prognosis

D. Hüseman · J. Gellermann · I. Vollmer · I. Ohde · S. Devaux
J.H.H. Ehrich · G. Filler (✉)
Department of Pediatric Nephrology, Charité,
Humboldt University, Schumannstrasse 20–21,
D-10117 Berlin, Germany
e-mail: guido.filler@charite.de
Fax: +49-030-2802-8844

Introduction

Diarrhea-associated hemolytic uremic syndrome (D+HUS) remains the most-common cause for acute renal failure in childhood. Various authors have reported a very high proportion of patients with renal sequelae and possible unfavorable long-term prognosis [1–4]. Several factors, including involvement of the central nervous system (CNS) and other extrarenal complications, leukocyte count at time of admission to hospital [5, 6], duration of anuria as early parameters [7, 8], and persistent proteinuria and hypertension [9, 10] as long-term parameters have been associated with a poor long-term prognosis. However, it is not yet clear what parameter should best be used to identify patients at risk. Hemodynamic changes leading to glomerular hypertension and hyperfiltration are assumed to be responsible for secondary and continuous impairment of glomerular integrity in patients with renal injury [11].

In this paper, we present evidence that determination of effective renal plasma flow (ERPF) in the 2nd year after onset of HUS can serve as an excellent parameter for identification of patients with poor long-term prognosis.

Patients and methods

Patients

The diagnosis of HUS was confirmed by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. D+ HUS was defined as HUS occurring after a diarrheal prodrome and having no recurrence [12].

A total of 165 patients with D+ HUS with a median age of 1.9 years (range 0.2–11.4 years) were treated at the Charité Children's Hospital, Humboldt University in Berlin between 1976 and 1995. Two further patients were excluded because of incomplete data.

According to Gianantonio et al. [3], D+ HUS patients were subdivided into three groups according to duration of anuria: no anuria or mild HUS (n=57, 3 fatal cases), anuria for 1–7 days or moderate HUS (n=49, 5 fatal cases), and anuria for 8–57 days (median 14.0) or severe HUS (n=54, 6 fatal cases). Five patients with duration of dialysis of 12, 13, 13, 27, and 38 days could not

be classified because the duration of anuria was not documented. Two of these died during the acute course.

After discharge from hospital, patients were regularly seen in the outpatient clinic and most had repeat investigations: 132 of 149 surviving patients were investigated 6 months after diagnosis of HUS, and 127 patients were followed for at least 2 years as outpatients or sent for consultant investigations by their physicians and were thus eligible for further analysis of long-term outcome. Median follow-up of the 127 patients was 5.0 years (range 2.0–13.2 years). There were 45 patients with mild D+ HUS, 35 with moderate D+ HUS,and 44 with severe D+ HUS. During the 1st year after onset of HUS, 10 patients were lost to follow-up and another 12 children were lost during the 2nd year. Reasons for terminating follow-up in our unit included apparent full recovery, long distance travel requirements, and/or in a few cases transfer to an adult nephrology unit.

Methods

A modified single-injection clearance method according to Blaufox and Potchen [13] and Chantler and Barratt [14] with simultaneous application of 80 kBq ^{51}Cr-EDTA and 15 kBq ^{123}iodine-hippurate per kilogram body weight was used for estimation of glomerular filtration rate (GFR) and ERPF [15, 16]. The modifications to the original methods were simultaneous injection of both substances and the clearance was determined by a single point serum concentration measurement of ^{51}Cr-EDTA and ^{123}iodine-hippurate at 30 min after injection and simultaneous determination of isotope activity count with two probes for detection of each tracer placed behind the child's thorax. The half-life of the decay of each isotope was calculated by a computer program from both the slope of the percutaneous measurement plotted on semilogarithmic paper and the single point serum concentration [14]. Values between 80 ml/min per 1.73 m^2 and 150 ml/min per 1.73 m^2 were defined as normal GFR [17]. ERPF values below 515 ml/min per 1.73 m^2 were previously defined as pathological [16]. Filtration fraction (FF) was calculated by GFR/ ERPF. Values above 0.19 were considered elevated. Recovery and impairment of renal function after HUS were investigated by analyzing 249 simultaneous clearance investigations during the 1st year and 375 clearances from 1 year until the end of follow-up of our surviving patients. In 9 of 127 cases at final classification, GFR was estimated using a length/creatinine ratio according to Schwartz et al. [18], because isotope clearance data were not available. Proteinuria was investigated by semiquantitative (dipstick) or quantitative analysis of random urine specimens obtained at the outpatient clinic (usually second morning voiding) and relevant proteinuria was defined as ≥1+ or ≥300 mg/l. Blood pressure (BP) was measured at every outpatient appointment, and after 1992, 24-h BP measurements were regularly conducted with our previously published normal values [19]. In most cases, antihypertensive therapy was instituted when the average BP was >95th percentile, and in this study, antihypertensive treatment served as an indicator of hypertension. Clinical data, such as need for antihypertensives, BP, leukocyte count, and duration of anuria were taken from the patients' inpatient files during the acute illness.

Renal function was classified as follows: group I with complete renal recovery (i.e., absence of proteinuria and hypertension and a GFR above 80 ml/min per 1.73 m^2); group II with moderate impairment of renal function (i.e., GFR between 60 and 80 ml/min per 1.73 m^2 and/or presence of proteinuria and/or need for antihypertensive therapy); group III with chronic renal failure (CRF, i.e,. GFR <60 ml/min per 1.73m^2); and group IV as end-stage renal disease (ESRD).

Statistical analysis

Data between two groups were compared with the unpaired *t*-test or with the Mann-Whitney test , and if Gaussian distribution could not be established by the Kolmogorow-Smirnow test. The Kruskal-Wallis-test was used for comparison of data between more than two groups. Categorical variables were compared using Fisher's exact test .

We calculated the probabilities for absence of sequelae by using Kaplan-Meier plots and compared survival curves with the log-rank test. To assess the diagnostic accuracy for detection of renal sequelae, duration of anuria, and ERPF and GFR in the 2nd year after diagnosis of HUS, receiver-operating characteristic (ROC) plots were constructed according to Zweig and Campbell [20]. ROC plots allow the simultaneous comparison of the diagnostic specificity and sensitivity of two variables over a wide range of hypothetical cut-off values. The resulting ROC plot areas were compared by nonparametric procedures [13].

Results

Early outcome

The clinical characteristics of our patients are shown in Table 1, with the patients grouped according to duration of anuria. During the 1st year after diagnosis, 138 pa-

Table 1 Clinical characteristics and long-term outcome of patients with diarrhea-associated hemolytic uremic syndrome (D+ HUS) according to duration of anuria (*CNS* central nervous system)

	Mild HUS	Moderate HUS	Severe HUS	Not classified
Total	57	49	54	5
Fatal cases	3	5	6	2
Survivors	54	44	48	3
Age at onset (years)[a]	2.2 (0.3–11.4)	1.8 (0.3–7.8)	1.8 (0.6–8.5)	2.1, 3.9, and 11.4
Antihypertensive therapy	10	11	25*	2
CNS complications	4	12	13	1
Leukocyte count (×10^9/l)[a]	14.7 (3.4–49.4)	15.2 (7.1–31.9)	19.7 (7.7–61.9)**	11.0, 14.2, and 14.3
Dialysis required	41	43	48	3
Lost to follow-up	9	9	4	0
Final outcome classification	45	35	44	3
Follow-up duration (years)[a]	4.9 (2.0–13.2)	5.0 (2.0–10.0)	5.0 (2.0–12.6)	4.0, 6.0, and 7.5
No sequelae	42	33	22	1
Moderate renal impairment	3	2	14	2
Chronic renal failure	0	0	4	0
End-stage renal disease	0	0	4	0

*P<0.001 vs mild HUS (Fisher's test); **P<0.05 vs mild HUS (Mann-Whitney test)
[a] Median (range)

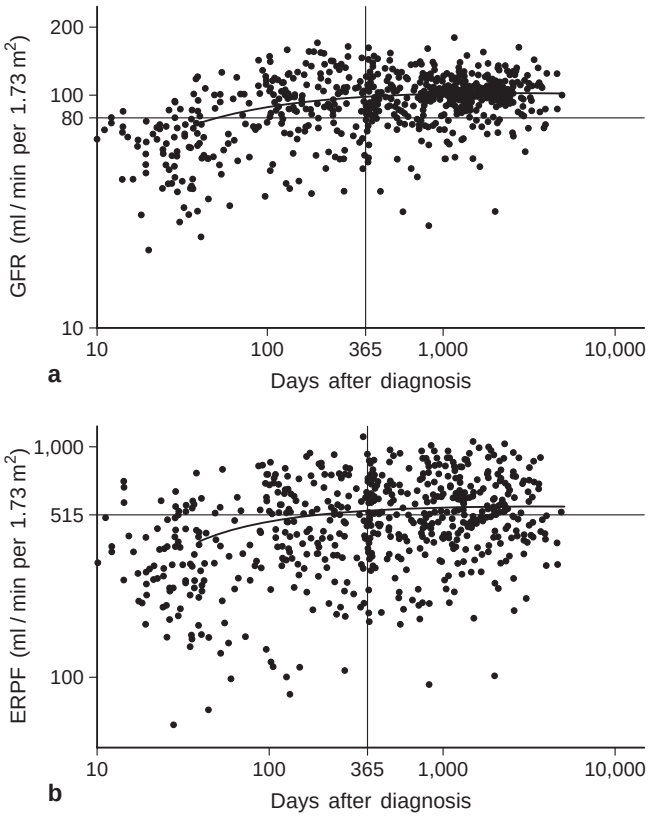

Fig. 1a, b Results of 634 ^{51}Cr-EDTA and ^{123}iodine-hippurate-clearances in 138 patients after diarrhea-associated hemolytic uremic syndrome (D+ HUS) for measurement of glomerular filtration rate (*GFR*) (**a**) and effective renal plasma flow (*ERPF*) (**b**). *Horizontal line*: lower reference limit. The fitted line was calculated by using nonlinear regression with a one-site binding hyperbola model (y=Const*x/(Const2+x))

tients underwent at least one clearance investigation. These early clearance data did not correlate with development or persistence of renal dysfunction. GFR and ERPF increased with time, reaching a plateau at about 1 year after diagnosis (Fig. 1a, b).

Long-term outcome

General findings

Long-term outcome was studied in 127 D+ HUS survivors who were followed for a median of 5 years (range 2–13 years). Ninety-eight patients belonged to group I (absence of renal sequelae, 77.2%), 21 patients to group II (moderate renal impairment, 16.5%), 4 patients belonged to group III (CRF, 3.2%), and 4 patients to group IV (ESRD, 3.2%) at the end of follow-up.

We analyzed the influence of duration of anuria, prevalence of hypertension, and CNS involvement during the acute phase on the probability of the absence of renal sequelae at last follow-up by Kaplan-Meier analysis. There was no statistically significant difference between patients with mild (no anuria) and moderate HUS (anuria

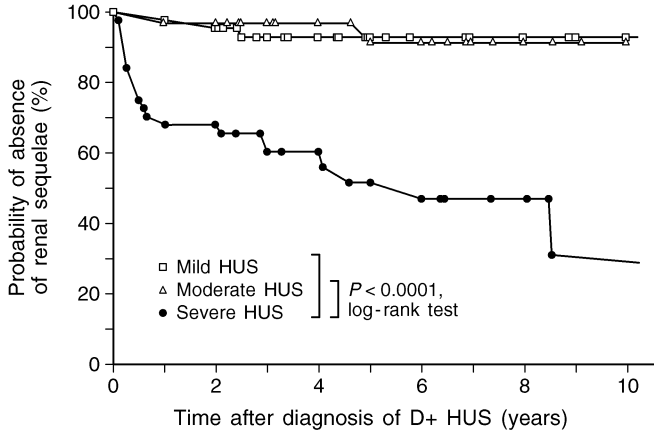

Fig. 2 Probability of absence of renal sequelae in patients (n=124) with a follow-up of 2–13 years (median 5 years). Mild HUS (no anuria), n=45, *open squares*; moderate HUS (anuria 1–7 days), n=35, *open triangles*; severe HUS (anuria >7 days), n=44, *closed circles*. There was a significant difference between patients with severe HUS and mild (P<0.0001, log-rank test) and moderate HUS (P<0.0001, log-rank test), respectively

for 1–7 days). In contrast, the probability of the absence of renal sequelae was significantly lower in patients with severe HUS (anuria >7 days) (P<0.0001, log-rank test, Fig. 2). The presence of hypertension during the initial phase also resulted in a significantly lower probability of absence of renal sequelae when compared with normotensive patients (P<0.0001, log-rank test). In the subgroup of patients with anuria for more than 7 days, hypertension during the acute phase was also associated with a lower probability of absence of renal sequelae (P<0.05, log-rank test). CNS involvement in the initial phase did not influence the development of renal sequelae.

Clearance results

Of 127 patients followed for at least 2 years, 110 underwent a clearance investigation 13–24 months after diagnosis of HUS. In these patients we studied the relationship between GFR and ERPF values in the 2nd year and the presence or absence of renal sequelae at the time of last follow-up (Table 2).

Median ERPF in patients without sequelae at end of follow-up (n=84) was 598 (range 210–1,100) ml/min per 1.73 m^2 in the 2nd year after diagnosis of HUS. This compares with a median ERPF of 362 (range 92–690) ml/min per 1.73 m^2 in the group of children with sequelae (n=26, P<0.0001, Mann-Whitney test). Of all patients with normal ERPF (>515, n=58), only 4 (6.9%) presented with sequelae at the end of follow-up, while patients with pathological ERPF (n=52) had a risk of 42.3% for final presence of renal sequelae (P<0.0001, Fisher's test).

GFR in the 2nd year was normal in 92 of 110 patients. In 13 patients GFR was between 60 and 80 ml/min per

Table 2 The relationship between clearance data 13 – 24 months after onset of D+ HUS and long-term outcome of 127 children with follow-up duration of 2.0–13.2 years (median 5.0 years) (*GFR* glomerular filtration rate, *ERPF* effective renal plasma flow, *FF* filtration fraction)

		Number	%	Outcome group at last follow-up				
				No sequelae	Moderate renal impairment	Chronic renal failure	End-stage renal disease	Probability of sequelae
Total *n*		127		98	21	4	4	22.8%
GFR	<60	5	4.5%	1	1	1	2	80.0%
	60–79	13	11.8%	5	5	2	1	61.5%
	≥80	92	83.6%	78	14	0	0	15.2%
ERPF	<450	36	32.7%	17	13	3	3	52.8%
	450–514	16	14.5%	13	3	0	0	18.8%
	≥515	58	52.7%	54	4	0	0	6.9%
FF	>22.0	35	31.8%	18	11	3	3	48.6%
	19.1–22.0	25	22.7%	22	3	0	0	12.0%
	≤19.0	50	45.5%	44	6	0	0	12.0%
No data		17		14	1	1	1	17.6%

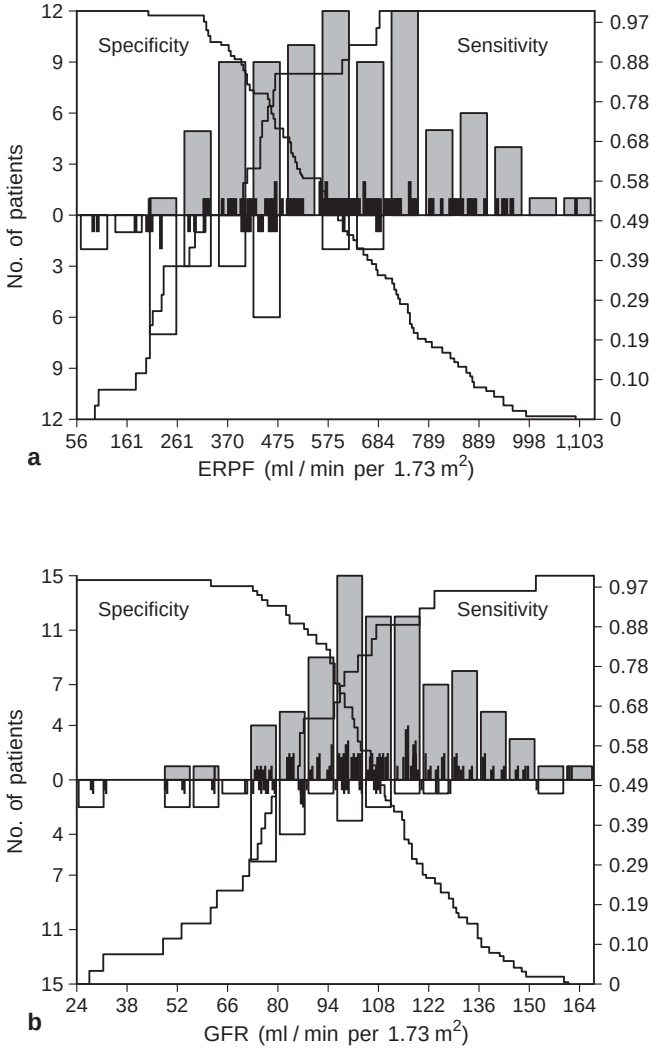

Fig. 3a, b Diagnostic sensitivity and specificity of ^{51}Cr-EDTA and ^{123}I-hippurate clearance results measured 13–24 months after onset of D+ HUS and outcome at least follow-up of 110 patients (median 5 years). *Below middle line and unshaded columns*: patients with sequelae; *above middle line* and *shaded* columns: patients without sequelae

1.73 m^2 and in 5 children <60 ml/min per 1.73 m^2. Of the 5 children with GFR <60 ml/min per 1.73 m^2, 2 progressed to ESRD after 2 and 12.5 years, respectively; 1 remained in compensated renal insufficiency; 1 temporarily improved to normal after 2.7 years and deteriorated again after 5 years, and the fifth recovered very slowly and maintained a stable GFR between 65 and 80 ml/min per 1.73 m^2 between 2.6 and 5.8 years after diagnosis of HUS, but regained a normal GFR after 7.4 years.

In the 2nd year after HUS, the proportion of children with normal ERPF (52.7%) was lower than the proportion with normal GFR (83.6%, P<0.0001, Fisher's test). The mean FF of patients with renal impairment at the end of follow-up was 0.26±0.07, significantly higher than patients without renal impairment (0.19±0.05, P<0.0001, t-test).

Figure 3a shows the diagnostic sensitivity and specificity for the GFR. There was considerable overlap of subjects with and without sequelae. Using the lower reference value of 515 ml/min per 1.73 m^2 as cut-off limit for ROC plot analysis, a diagnostic sensitivity of 85% with a specificity of 64% was achieved (Fig. 3b). The only 4 patients with normal ERPF in the 2nd year, but with renal impairment at the end of follow-up, presented with mild proteinuria between 300 and 1,000 mg/l in 3 cases and with hypertension in the fourth. GFR at the end of follow-up was normal in all of these 4 patients (range 107–149 ml/min per 1.73 m^2). In order to compare the diagnostic value, a plot of 1-specificity versus sensitivity for the best parameters (duration of anuria, GFR in the 2nd year, and ERPF in the 2nd year) is given in Fig. 4. The area under the curve reflects the diagnostic value. Areas (standard errors) were 0.84 (0.04) for ERPF, 0.83 (0.05) for duration of anuria, and 0.79 (0.06) for GFR (Fig. 4). We found a statistically significant difference between the diagnostic value of ERPF and GFR (P<0.05) for the null hypothesis that ERPF is a better marker than GFR.

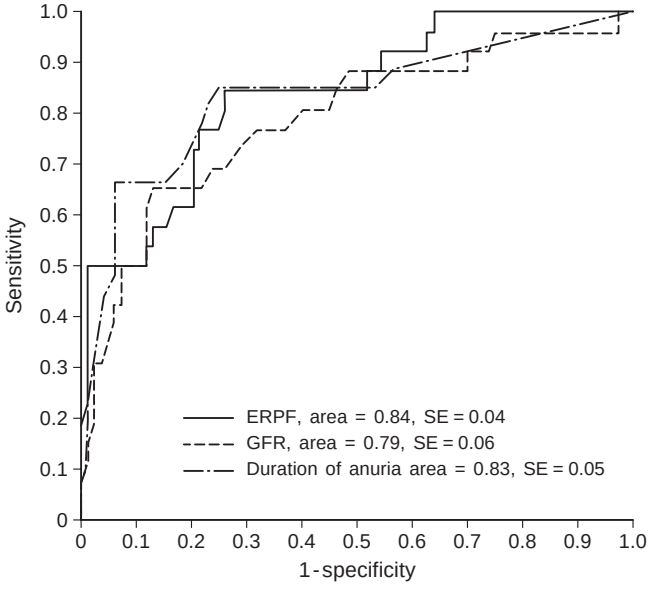

Fig. 4 Analysis of the diagnostic value of clinical features for detection of patients with poor long-term outcome. The difference between the diagnostic value of GFR and ERPF was statistically significant ($P<0.05$, χ^2test)

Discussion

D+ HUS remains the most-common cause of acute renal failure in childhood. Acute mortality was reduced worldwide from about 15% in the 1970s [3, 21] to below 5% [1, 2, 22], following improvement of diagnosis and therapeutic management, including dialysis [12]. In contrast, "survival during the acute phase of HUS has created a new chronic renal disease," as first described by Gianantonio et al. [23] with an unfavorable long-term prognosis. Our observations confirm the existence of three groups of patients: the first group does not recover from early renal injury, the second shows complete and sustained recovery, and the third group shows a temporary improvement or even normalization of renal function with a secondary deterioration due to slowly progressive nephropathy. The major task of this retrospective analysis was to detect early signs of occult nephropathy and thus identify risk factors for a poor renal prognosis, particularly in the third group. Indicators of renal sequelae included proteinuria, hypertension, and a reduced GFR.

At the end of a median follow-up of 5.0 years, the proportion of children with clinical signs of renal impairment was 23%, which was lower than reported in several other recent studies, including studies from Germany [1, 2, 4, 8, 10, 24]. A similar prevalence of sequelae was documented by Kelles et al. in 1994 [22] and by de Jong and Monnens in 1988 [21]. Differences may be partly due to the fact that some investigators included D- HUS patients, who have a poorer prognosis [25]. Underestimation of the proportion of patients with renal impairment is also due to the rather short follow-up period. In the longest analysis published to date, Gagnadoux and Habib [26] found secondary deterioration of renal function even beyond 10 years after onset of HUS. We fear that patients with reduced ERPF may be especially likely to develop sequelae during further follow-up.

The duration of anuria in the acute phase has been identified as an important predictor of outcome in various studies [2, 7, 8]. In this study, we confirmed this and found a cut-off interval of 7 days of anuria a good prognostic indicator. Despite the confirmed importance of the duration of anuria, 6.7% of patients without anuria developed nephropathy in the follow-up period, and 5.7% of patients with a duration of anuria between 1 and 7 days also developed renal sequelae.

The presence of hypertension during the acute phase was also a predictor of poor long-term outcome. During the acute phase, 52% of patients with severe HUS required antihypertensive therapy. The surviving children from this group had a significantly higher risk for developing renal sequelae than children with severe HUS who did not require antihypertensive therapy early in the disease. This is not an established risk factor, and one might argue whether hypertension in the acute phase merely reflects fluid overload or the severity of the renal injury. It remains to be established whether the hypertension per se was responsible for the unfavorable outcome.

Clearance investigations during the 1st year after diagnosis of HUS were too early to serve as a diagnostic tool for long-term outcome. The data showed a continuous improvement of both GFR and ERPF up to 1 year after diagnosis of HUS, and therefore we conclude that there is no need for a clearance study in the 1st year.

Clarification of the pathophysiology of secondary deterioration is important for the early identification of patients with progressive renal disease and, more importantly, for possible therapeutic interventions for prevention [27]. Brenner et al. [28, 29] presented evidence that reduction of nephron mass in various animal models caused glomerular hyperfiltration and glomerular hypertension as adaptive mechanisms. Unfortunately, this adaptation seems to initiate or potentiate progressive glomerular damage. Microalbuminuria is a recognized marker of hyperfiltration [30] and is an established diagnostic tool in former HUS patients [9]. In this study, microalbuminuria was not measured in all patients. Perelstein et al. [31] detected a loss of renal functional reserve in patients with a history of HUS and normal serum creatinine, similar to patients with unilateral nephrectomy, and concluded that hyperfiltration of the remaining nephrons could be a factor in the progression of the chronic renal disease in these patients. Renal biopsies in patients with signs of renal impairment after HUS showed glomerular lesions unrelated to HUS but rather related to various renal diseases leading to a reduction of functioning nephron mass [32, 33].

Our clearance data revealed hemodynamic changes in about half of our patients in the 2nd year after HUS. ERPF and FF were abnormal in 47% and 54%, respectively, while GFR was normal in 84% at the same time. Although the extent to which the extraction is disturbed

in patients with renal injury is unknown, and thus the real renal plasma flow differs from the effective plasma flow, ERPF measurements remain a useful estimate [34]. According to the hyperfiltration theory, these functional changes might be an early step in the progressive loss of renal function. All but 4 of the patients who developed or retained renal sequelae during the observation period had a decreased ERPF in the 2nd year. These findings support the hypothesis that the surviving nephrons after HUS undergo hyperfiltration, leading to secondary deterioration of renal function in the absence of a new injury. Our findings suggest that ERPF is a good marker for the recovered nephron mass and therefore reflects the risk for developing secondary deterioration of renal function or aggravation of nephropathy. The investigation is easy to perform, requires only 1 h for analysis, and relies on low doses of radioactive isotope. Therefore we recommend performing a ^{123}iodine-hippurate clearance in the 2nd year after diagnosis of D+ HUS to identify patients at high risk for developing progressive renal disease.

References

1. Fitzpatrick M, Shah V, Trompeter RS, Dillon MJ, Barratt M. (1991) Long term renal outcome of childhood haemolytic uraemic syndrome. BMJ 303:489–492
2. 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
3. Gianantonio CA, Vitacco M, Mendilaharzu F, Gallo G (1968) The hemolytic-uremic syndrome. Renal status of 76 patients at long-term follow-up. J Pediatr 72:757–765
4. O'Regan S, Blais N, Russo P, Pison CF, Rousseau E (1989) Hemolytic uremic syndrome: glomerular filtration rate, 6 to 11 years later measured by 99mTc DTPA plasma slope clearance. Clin Nephrol 32:217–220
5. Walters MDS, Matthei U, Kay R, Dillon MJ, Barratt TM (1989) The polymorphonuclear leucocyte count in childhood haemolytic uraemic syndrome. Pediatr Nephrol 3:130–134
6. Fitzpatrick MM, Shah V, Filler G, Dillon MJ, Barratt TM (1992) Neutrophil activation in the haemolytic uraemic syndrome: free and complexed elastase in plasma. Pediatr Nephrol 6:50–53
7. Robson WLM, Leung AKC, Brant R (1993) Relationship of the recovery in the glomerular filtration rate to the duration of anuira in diarrhea-associated hemolytic uremic syndrome. Am J Nephrol 13:194–197
8. 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
9. Milford DV, White RHR, Taylor CM (1991) Prognostic significance of proteinuria one year after onset of diarrhea-associated hemolytic uremic-syndrome. J Pediatr118:191–194
10. Tönshoff B, Sammet A, Sanden I, Mehls O, Waldherr R, Schärer K (1994) Outcome and prognostic determinants in the hemolytic uremic syndrome of children. Nephron 68:63–70
11. Buckalew VM (1994) Pathophysiology of progressive renal failure. South Med J 87:1028–1033
12. Kaplan B, Trompeter RS, Moake JL (1992) Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Dekker, New York
13. Blaufox MD, Potchen J (1965) Measurement of effective renal plasma flow in men by external counting methods. Clin Res 13:302
14. Chantler C, Barratt TM (1972) Estimation of glomerular filtration rate from plasma clearance of 51-chromium edetic acid. Arch Dis Child 47:613–617
15. Gellert S, Devaux S (1994) Hypertrophy of transplanted kidney, depending on donor and recipient age and immunosuppressive therapy. Transplant Proc 26:13–14
16. Gellert S, Devaux S, Schoenberger B, Mai G (1996) Donor age and graft function. Pediatr Nephrol 10:716–719
17. Filler G, Witt I, Priem F, Ehrich JHH, Jung K (1997) Are cystatin C and b2-microglobulin better markers than serum creatinine for prediction of a normal glomerular filtration rate in pediatrics? Clin Chem 43:1077–1078
18. Schwartz GJ, Haycock GB, Edelmann CM, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58:259–263
19. Gellermann J, Kraft S, Ehrich JHH (1997) Twenty-four-hour ambulatory blood pressure monitoring in young children. Pediatr Nephrol 11:707–710
20. Zweig MH, Campbell G (1993) Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem 39:561–577
21. Jong M de, Monnens L (1988) Haemolytic-uraemic syndrome: a 10-year follow-up study of 73 patients. Nephrol Dial Transplant 3:379–382
22. Kelles A, Van Dyck M, Proesmans W (1994) Childhood haemolytic uraemic syndrome: long-term outcome and prognostic features. Eur J Pediatr 153:35–42
23. Gianantonio CA, Vitacco M, Mendilaharzu F, Gallo G, Sojo ET (1973) The hemolytic-uremic syndrome. Nephron 11:174–192
24. Wende-Fischer R, Hoyer PF, Offner G, Brodehl J (1996) Hämolytisch-urämisches Syndrom im Kindesalter. Monatsschr Kinderheilkd 144:526–533
25. Renaud C, Niaudet P, Gagnadoux MF, Broyer M, Habib R (1995) Haemolytic uraemic syndrome: prognostic factors in children over 3 years of age. Pediatr Nephrol 9:24–29
26. Gagnadoux MF, Habib R (1995) Long-term prognosis of childhood hemolytic-uremic syndrome J Nephrol 8:87–92
27. Brenner BM, Lawler EV, Mackenzie HS (1996) The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int 49:1774–1777
28. Brenner BM, Meyer TW, Hostetter TH (1982) Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 307:652–659
29. Brenner BM, Mackenzie HS (1997) Nephron mass as a risk factor for progression of renal disease. Kidney Int [Suppl] 63:S124–S127
30. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud R, Keen H (1982) Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet I:1430–1432
31. Perelstein EM, Grunfeld BG, Simsolo RB, Gimenez MI, Gianantonio CA (1990) Renal functional reserve compared in haemolytic uraemic syndrome and single kidney. Arch Dis Child 65:728–731
32. Caletti MG, Gallo G, Gianantonio CA (1996) Development of focal segmental sclerosis and hyalinosis in hemolytic uremic syndrome. Pediatr Nephrol 10:687–692
33. Moghal NE, Ferreira MA, Howie AJ, Milford DV, Raafat F, Taylor CM (1998) The late histological findings in diarrhea-associated hemolytic uremic syndrome. J Pediatr 133:220–223
34. Battilana C, Zhang HP, Olshen RA, Wexler L, Myers BD (1991) PAH extraction and estimation of plasma flow in diseased human kidneys. Am J Physiol 261:F726–733