

Long-term course and mechanisms of progression of renal disease in hemolytic uremic syndrome

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Long-term course and mechanisms of progression of renal disease in hemolytic uremic syndrome. In the classic form of hemolytic uremic syndrome associated with toxins of gram-negative enterobacteria, mortality in the acute stage has been lower than 5% since 1978 (data from the Nephrology Committee, Argentine Society of Pediatrics). Children usually die because of severe involvement of the central nervous system, intestine, or myocardium and its complications, or because of intercurrent infection. Treatment in this phase is supportive, and efforts should be put into prevention of infection by Shiga-like toxin-producing enterohemorrhagic *Escherichia coli*.

Of the 95% who survive, approximately one third is at risk for having chronic sequelae. Motor, sensory, or intellectual deficits, intestinal strictures, myocardial infarctions, or diabetes are infrequent. The more-frequent chronic renal lesion is characterized by the hyperfunction of nephrons remaining after the acute necrotizing lesion, which leads to progressive scarring, and not by persistence or recurrence of the microangiopathic process.

Three courses of progression to end-stage renal failure have been described. Children with most severe forms do not recover from acute renal failure and enter directly into a dialysis and transplantation program. A second group recovers renal function partially, with persistent proteinuria and frequently hypertension; progression to end-stage renal failure occurs in 2 to 5 years. The third group may recover normal serum creatinine and creatinine clearance, with persistent proteinuria. They are at risk of progressing to chronic renal failure and end-stage renal disease after more than 5 years, and sometimes as late as 20 years, after the acute disease. Treatment should aim at preventing the mechanisms associated with progressive renal scarring. Transplantation is indicated in this form of hemolytic uremic syndrome, because there is little, if any, risk of recurrence, and the prognosis is similar to that of transplantation for other diseases.

Resumen

En la forma clásica del Síndrome Hemolítico Urémico (SHU) asociado a toxinas de enterobacterias gram negativas, la mortalidad en la fase aguda ha sido menor al 5% desde 1978. Las causas de muerte se deben a complicaciones neurológicas, intestinales, cardíacas o a infecciones intercurrentes. Del 95% restante, aproximadamente un 30% están en riesgo de desarrollar secuelas crónicas. La lesión renal más frecuente se debe a hiperfiltración de las nefronas remanentes, lo cual conduce

a fibrosis progresiva, y no a la persistencia o recurrencia de la enfermedad microangiopática.

Su curso clínico puede seguir tres caminos. En el primero, los niños con las formas más severas nunca se recuperan de la fase aguda y pasan directamente a diálisis y trasplante; un segundo grupo recupera parcialmente la función renal, presenta albuminuria persistente e hipertensión y desarrolla insuficiencia renal crónica en un lapso de 2 a 5 años. Finalmente, en un tercer grupo, las cifras de creatinina sérica y la depuración de creatinina regresan a la normalidad, con albuminuria persistente y se encuentran en riesgo de desarrollar insuficiencia renal crónica después de cinco, o en algunos casos, hasta veinte años después de la fase aguda. El tratamiento se debe orientar a prevenir los mecanismos de la progresión del daño renal. Se requieren de estudios a largo plazo para evaluar estos tratamientos, así como el mejor momento de utilizarlos. El trasplante renal está indicado en esta forma de SHU, ya que el riesgo de recurrencia es mínimo y la supervivencia del injerto es similar al observado en otras patologías.

Hemolytic uremic syndrome (HUS) is a systemic thrombotic microangiopathy (TMA) caused by different etiologies and mechanisms (Table 1), which results in endothelial lesions leading to thrombosis of the microcirculation in most organs. The most frequent cause in pediatrics is a lesion due to the effect of toxins of a group of enterobacteria, enterohemorrhagic *Escherichia coli*, usually presenting with diarrhea (D+, epidemic, enteropathic, typical). Studies of large groups of patients have shown that it behaves as a “one-shot disease,” causing necrotic lesions in the kidney, intestine, central nervous system (CNS), pancreas, myocardium, and liver. Hemolytic anemia, on the other hand, resolves after the acute stage.

POST-ACUTE COURSE

More than 95% of children recover from the acute phase [1]. Lesions in organs other than the kidney depend on the magnitude of the acute insult, because typically the disease mechanism is not persistent or recurrent. CNS sequelae are infrequent [2, 3], and chronic lesions in the colon, pancreas, and liver are reported occasionally [3, 4]. Residual kidney involvement, on the other hand,

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Table 1. Hemolytic uremic syndrome: Clinical entities

Group	Causes	Denomination
Associate to infections	Bacterial cytotoxin (<i>E. coli</i> , <i>Shigella</i> , <i>Salmonella</i>), pneumococcal neuraminidase, viral, microtobiote, etc.	Epidemic, "classical" D+, enteropathic
Idiopathic	Related to primary endothelial dysfunction?	Hereditary, (autosomic recessive, autosomic dominant), sporadic, atypical
Genetic	Complement factor H von Willebrand factor protease	Recurrent TTP
Immunologic	von Willebrand factor protease Ab	
Associated with systemic diseases or other precipitating factors	Cancer, pregnancy, malignant hypertension, transplant rejection, glomerulopathies	
Toxics	Cyclosporine, tacrolimus, mitomycin, radiation	

TTP, thrombotic thrombocytopenic purpura.

is seen in about one third of those who recover from the acute phase.

FOLLOW-UP OF THE KIDNEY LESION

After more than 1 year of follow-up, a patient with normal serum creatinine (SCr) and/or creatinine clearance (Ccr), normal blood pressure, and normal urinalysis is considered "cured." Yet some studies have documented the presence of microalbuminuria or lack of "functional reserve" after protein loads. This group accounts for 49% of a cohort of 208 children at 1 year after the acute stage. At 3 years' follow-up, 62% (128) were still in this group, which shows that some patients were still recovering from the acute insult after the first year [5]. In 118 patients followed up for more than 10 years, the proportion did not change [6]. Some patients presented normal SCr or Ccr and persistent proteinuria with or without hypertension. Most of them, followed for some time without treatment, showed deterioration of glomerular filtration rate. This group was 6% at 1 year, 14% at 3 years, and 18% after more than 10 years of follow-up. A third group presented decreased Ccr or increased SCr, with different degrees of persistent proteinuria (which may be in the nephrotic range) and frequently hypertension. At 1 year, 45% of the children belonged to this group, decreasing to 24% at 3 years and 19% after more than 10 years. (Fig. 1) Within this group, some patients were in end-stage renal failure (ESRF). A small proportion of them never recovered completely from acute renal failure, developing ESRF an average of 4 years after the acute illness. The majority recovered normal SCr, arriving at ESRF after an average of 9.8 years, and as long as 22 years of follow-up [5].

Studies from around the world have shown a similar proportion after the same course, when the description of the acute episode shows that most of the patients had a form of HUS associated with Shiga-like toxin (SLT) [7–10]. Although the most recent metaanalysis used a different schema, the proportion of those "cured" was similar [11].

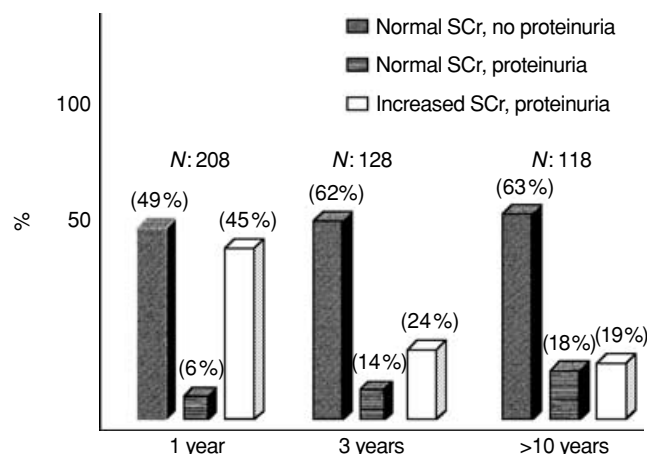


Fig. 1. Renal status at 1, 3, and >10 years of follow-up after acute HUS.

MECHANISM OF PROGRESSION

Several years ago, we suggested that patients with HUS whose renal function deteriorated after a period of normal function (as measured by SCr or Ccr) did so because of hyperfunction of the remaining nephrons—the disease being a clinical model of the classical mechanism of progression of chronic renal failure [12]. Three lines of research have registered data compatible with this hypothesis. In our study, 4 of 12 patients with normal Ccr many years after the acute stage were unable to increase their inulin clearance when challenged with protein loads. One possible interpretation is that they were using their "functional reserve" in the presence of a reduced nephron mass. The maximal filtration capacity after the protein load in the 12 patients was 84.9 mL/min/1.73m², significantly lower than that in the normal controls (154.7 mL/min/1.73m²) ($P < 0.025$) [12] (Fig. 2).

The second evidence for hyperfiltration injury was the demonstration that some children had microalbuminuria with normal clinical and laboratory findings years after an acute episode of HUS. The authors speculated that it could be a predictor of progressive lesions, similar to other renal diseases [13].

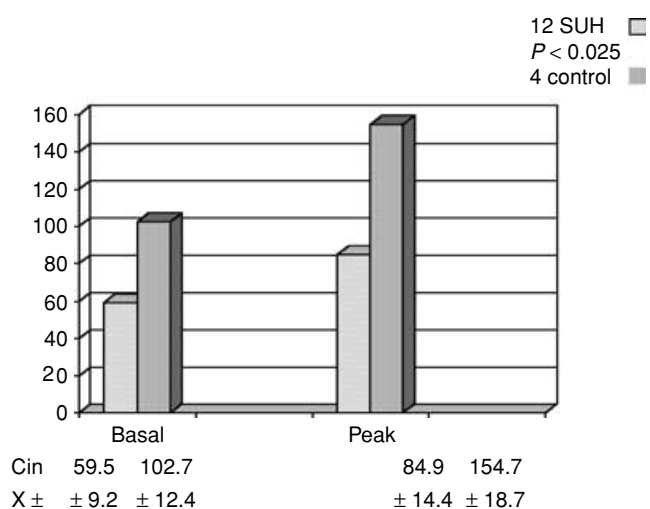


Fig. 2. Mean C_{IN} before and 3 hours after a protein load in patients with HUS at follow-up. C_{IN} , inulin clearance.

A third line of inquiry was reported in the study of sequential biopsies in which the proportion of glomeruli involved in the acute insult was the same as that of scarred glomeruli later [14]. Histologic changes in patients with chronic renal sequelae show focal and segmental sclerosis and mesangial expansion in the glomeruli [15]. These observations also suggest the mechanism of residual hyperfunction as the cause of progressive scarring and loss of renal function.

In this respect, the finding that acute stage HUS is associated with increased risk of chronic disease suggests a more severe acute systemic microangiopathic process. The presence of anuria, its duration, and the need and duration of dialysis are variables reported to predict long-term outcome [6–10]. Persistent hypertension after the recovery of diuresis also points to an increased risk of chronic lesions [5]. Several extrarenal manifestations, probably reflecting a more severe diffuse microangiopathic process, such as marked CNS [8, 10] and intestinal symptoms [15], are also associated with a poor long-term prognosis. The importance of age at onset is controversial. Although a recent report suggests that older children might have a poorer prognosis [17], other authors conclude that there is no difference in outcome [18].

MANAGEMENT OF CHRONIC RENAL DISEASE IN HUS

Treatment in the acute stage of SLT-associated disease is supportive, but greater efforts should be put into prevention. The high incidence in Argentina is due to the large numbers of cattle colonized with enterohemorrhagic *Escherichia coli* that produce SLT-2, which has been shown to be more toxic. Control of production, distribution, and expenditure of meat and other cattle prod-

Table 2. Causes leading to terminal renal failure in a cohort of 200 consecutive children who had received transplants

Diseases	Number of patients	%
Uropathy	81	40
Glomerulonephropathy	39	19.5
Hemolytic uremic syndrome	31	15.5
Primary nephritic syndrome with focal and segmental glomerulosclerosis	21	11
Hypodysplasia	11	5.5
Interstitial nephropathy	7	3.5
Neurogenic bladder	5	2.5
Polycystic kidney	3	1.5
Cystinosis	2	1
Total	200	100

ucts, public education on the handling and processing of meals, and development of vaccines are actions that could decrease the frequency of this endemic disease.

Knowing the risks for chronic sequelae, close follow-up is required. Frequent controls of blood pressure and presence of proteinuria are mandatory. Although evidence for controlling the mechanisms of progression by interfering with the activity of angiotensin II is circumstantial and mostly extrapolated from other renal diseases by speculating the existence of a similar mechanism, control of hypertension to average or low-normal values, and treatment of proteinuria persisting for 6 months after the acute period with ACE inhibitors is recommended. One prospective, controlled, multicenter study aiming to demonstrate the effect of enalapril and losartan (an angiotensin II receptor blocker) on proteinuria is being performed in Argentina. Also, studies on the effect of these drugs on microalbuminuria detected in the late course of HUS should be planned.

HUS accounts for about 15% of children who enter ESRF in Argentina (Table 2). Renal transplantation is the preferred treatment modality for the disease associated with SLT. Although some reports have described recurrence in the graft [19], in large groups of children with the postdiarrheal HUS, no recurrence has been documented [5, 20].

Three problems complicate an analysis of the risk of recurrence of HUS in a transplanted kidney: (1) TMA can be the pathologic pattern of acute immunologic rejection. (2) TMA has been seen in renal allografts in patients receiving calcineurin inhibitors whose original disease was not HUS and in patients with bone marrow or liver transplantation. (3) Recurrence has been reported predominantly in older children and adults, and in patients with familial, recurrent, or nonpostdiarrheal (D-) forms of HUS.

In our own experience with transplantation after HUS, only 1 patient lost his graft after 2 months. He was an 8-year-old boy who had severe D- HUS, without recovering from acute renal failure. Five years earlier, his brother

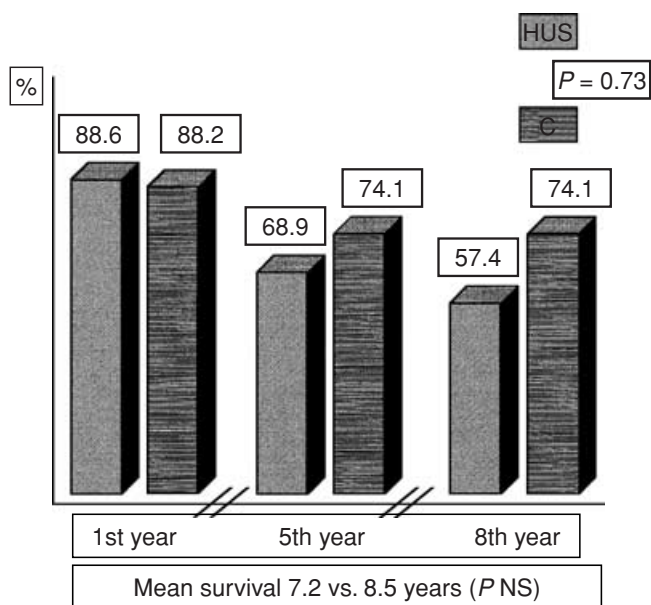


Fig. 3. Actuarial survival of grafts in patients with HUS and without HUS.

had had equally severe D-HUS. In reviewing the course of 23 renal transplants in 20 children whose original disease had been HUS, 16 presented with the classic epidemic type, receiving 19 grafts. The survival of functioning grafts, maintenance of stable renal function, incidence of acute rejection (AR), and prevalence of proteinuria and hypertension were compared with the same variables in a randomly selected group of 19 children who received renal transplants because of ESRF not due to HUS. Mean follow-up was 5 years, with a range of 1 to 11 years. Actuarial survival of grafts and of grafts with normal SCr was similar in the 2 groups ($P = 0.73$ and 0.27 , respectively, log-rank test) (Figs. 3 and 4). Mean survival of the grafts was 7.16 in the HUS group versus 8.53 years in the controls ($P = NS$) (Fig. 3). Mean survival with normal SCr was 2.07 in the HUS group versus 2.71 in the controls ($P = NS$) (Fig. 4). There were 14 ARs in the HUS group versus 8 ARs in the controls ($P = NS$). Prevalence of proteinuria and hypertension at 1 and 5 years' post-transplantation was similar for both groups. No evidence of TMA was seen in the 6 grafts biopsied for other indications [4]. In an extended review, including 25 patients with classic HUS, there were no changes in the results of the analysis (Table 3).

We conclude that patients who receive renal transplants for classic epidemic HUS have a very low risk of recurrence and that the long-term outcome of grafts is not different from that in patients with ESRF from other causes. Moreover, the use of calcineurin inhibitors in these patients does not seem to increase the risk of recurrence. Live related or cadaveric transplantation remains the treatment of choice for children who had this

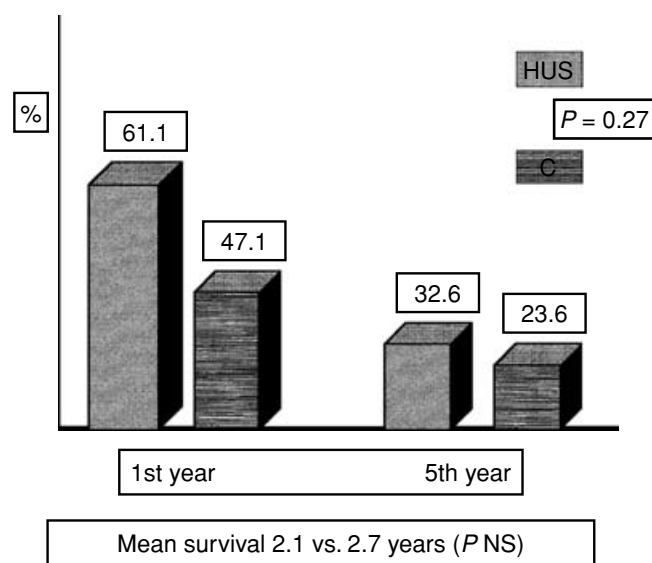


Fig. 4. Actuarial survival of grafts with normal SCr (diagonal lines, HUS; horizontal lines, non-HUS).

Table 3. Incidence of AR and prevalence of hypertension and proteinuria

	HUS	Controls	P value
AR	15	10	NS
Hypertension, first year	5/26	5/26	NS
Hypertension, fifth year	3/10	3/9	NS
Proteinuria, first year	7/26	6/26	NS
Proteinuria, fifth year	4/10	2/7	NS

Abbreviations are: AR, acute rejection, HUS, hemolytic uremic syndrome.

type of HUS. The most recent review of the literature of the risk of recurrence found only 1 (0.8%) reported recurrence in 118 children who had postdiarrheal HUS, 13 recurrences in 63 transplanted patients for D-HUS of unknown mechanism, and 18 recurrences in those with HUS associated with factor H deficiency, constitutional deficiency of von Willebrand factor-cleaving protease, or autosomal-dominant/recessive forms of HUS [20]. More studies on the long-term course of these treatments and the best time to use them are needed.

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