Epidemic hemolytic-uremic syndrome in children

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Hospital Nacional Prof. A. Posadas, and University of Buenos Aires School of Medicine, Buenos Aires, Argentina

CASE PRESENTATIONS

Patient 1. An 18-month-old girl presented with paleness and oliguria preceding by non-bloody diarrhea that had started five days previously. On admission, her blood pressure was 120/85 mm Hg (90th percentile, 105/68 mm Hg) and she was anuric. Her blood urea concentration was 168 mg/dl and hematocrit 22%; a blood smear contained numerous fragmented erythrocytes. Her serum electrolytes were: sodium, 132 mEq/liter; potassium, 5.8 mEq/liter; chloride, 102 mEq/liter; and bicarbonate, 15.2 mEq/liter. A diagnosis of the acute hemolytic-uremic syndrome (HUS) was made. She received one packed red blood cell transfusion. After three days of anuria and with her blood urea level reaching 285 mg/dl, peritoneal dialysis was started. Her anuria persisted for five days and she was discharged after two weeks, normotensive with a blood urea of 68 mg/dl and a serum creatinine of 0.85 mg/dl. On followup she remained normotensive; her urea was 19 mg/dl one month after the beginning of the acute disease. Her serum creatinine concentration was normal (0.6 mg/dl) at one year followup, but she still had proteinuria of 100 mg/dl in the first morning sample. Subsequent measurements revealed decreased proteinuria, which became intermittent after four years and has remained absent since the eighth year of followup. Her last evaluation, 13 years after the acute illness, revealed a normal adolescent girl, with normal growth and development; a blood pressure of 110/65 mm Hg; serum creatinine concentration, 0.8 mg/dl; and a normal urinalysis.

Patient 2. A 7-month-old boy was admitted to the hospital because of diarrhea over five days with bloody striae over the last two days. She was pale and irritable. Her blood pressure was 127/82 mm Hg (90th percentile, 105/69 mm Hg). She had been anuric for two weeks.

Her blood chemistries on admission were: hematocrit, 18%; urea, 95 mg/dl; serum creatinine, 3.6 mg/dl; sodium, 132 mEq/liter; potassium, 5.8 mEq/liter; chloride, 104 mEq/liter; bicarbonate, 15 mEq/liter; and platelet count, 86,000/mm 3. The peripheral blood smear showed anisocytosis, poikilocytosis, and fragmented red cells. The diagnosis of acute HUS was made. She was discharged after three weeks with a blood urea of 105 mg/dl. A low-protein diet and salt restriction were prescribed, as was alphamethyl dopa for his hypertension. When she was 4 years, 4 months old, she received her mother's kidney.

The child was followed as an outpatient, and she required propranolol to keep her blood pressure under control. She had persistent proteinuria, and her blood urea concentration remained between 80 mg/dl and 100 mg/dl even with protein restriction. Her serum creatinine level remained elevated and increased slowly until 2 years and 9 months after the acute episode (Fig. 2). When she was 4 years, 4 months old, she received her mother's kidney. Immunosuppressive medication consisted of prednisone and azathioprine; she had no acute rejection. One month post transplantation, her blood pressure was 120/75 mm Hg while she was receiving propanolol, her serum creatinine was 0.4 mg/dl, and her blood urea was 19 mg/dl. Five months after transplantation, her antihypertensive medication was withdrawn. She remained in good health, growing adequately and leading a normal life. At last followup, 12 years and 10 months after transplantation, this 17-year-old girl's height is 151 cm and her blood pressure is 120/75 mm Hg without antihypertensive medication. Her serum creatinine level is 0.92 mg/dl, with an estimated creatinine clearance of 90 ml/min/1.73 m 2.

DISCUSSION

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Table 1. Pathogenesis of HUS

<table>
<thead>
<tr>
<th>Associated with infection</th>
<th>Idiopathic or “atypical”</th>
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<tbody>
<tr>
<td>Bacterial cytotoxin (E. coli, Shigella, Salmonella)</td>
<td>Sporadic</td>
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<tr>
<td>Pneumococcal neuraminidase</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Viral</td>
<td>Hereditary</td>
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<tr>
<td>Associated with systemic conditions</td>
<td></td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Pregnancy</td>
<td></td>
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<tr>
<td>Malignant hypertension</td>
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<td>Transplant rejection</td>
<td></td>
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<tr>
<td>Glomerulonephritis</td>
<td></td>
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<tr>
<td>Exposure to toxins</td>
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<tr>
<td>Cyclosporine</td>
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<td>Mitomycin</td>
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<td>Radiation</td>
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</table>

Medical School, Buenos Aires, Argentina): The hemolytic-uremic syndrome was first described by Gasser et al more than 40 years ago [1]. Since then, several studies have established the multisystemic character of the thrombotic microangiopathy that constitutes the basic anatomic lesion of HUS [2–4]. In 1978, Kaplan and Drummond emphasized the different clinical entities that can present as this syndrome [5]: idiopathic sporadic or epidemic forms, syndromes occurring post pregnancy or oral contraceptive use, a lesion associated with infection, a familial or hereditary syndrome, and post-renal-transplantation HUS. With our current knowledge, I believe that these entities can be classified as (1) HUS associated with infections, including the “classic” epidemic (enteropathic) form with its high prevalence in children; (2) idiopathic HUS, which can be hereditary or sporadic, and probably is related to primary endothelial dysfunction; (3) HUS associated with systemic diseases or other precipitating factors; (4) and HUS resulting from exposure to toxins (drugs or radiation) (Table 1).

In children, the epidemic form can be difficult to differentiate from the “atypical” or idiopathic form. An intrinsic defect in the different endothelial functions that protect the microvasculature from thrombosis is the generally accepted hypothesis for the latter [6]. The definition generally used for its diagnosis requires the absence of gastrointestinal symptoms in the prodromic phase [7]. As we will see when I speak of epidemiology, a small group of children with evidence of verotoxin-producing E. coli (VTEC) infection does not have diarrhea at presentation and may be erroneously classified as “atypical.” One subgroup encompasses children who suffer one or more recurrences [8]. These children have a higher incidence of affected siblings, a high mortality rate, and a high chance of recurrence in the transplanted kidney [9]. In some of these patients, hypocomplementemia characterized the recurrence [10, 11]. Finally, an extensive analysis of the familial forms can be found in a chapter by Kaplan [12]. Some of these children have the HUS associated with verotoxin due to home contact. Others have hereditary forms; in these cases disease recurrence, hypocomplementemia, or recurrence in the renal graft is common, and they are included within the idiopathic HUS. For the purposes of this Forum, I will limit our discussion to the classic epidemic form.

When I was a resident in pediatrics in Argentina at the beginning of the 1960s, we interpreted the clinical picture in these infants as due to sepsis of gastrointestinal origin. We believed the anemia and thrombocytopenia to be part of the disseminated intravascular coagulation and the renal insufficiency to be due to acute tubular necrosis. The syndrome had been described in 1955 in a Swiss journal [1], but not until 1962 was the Argentine experience with HUS presented in a paper on acute renal failure (ARF) [13]. Gianantonio, to whom we are paying homage in this Forum, and his coworkers from the Children’s Hospital of Buenos Aires, published the first complete description of the clinical features and evolution of the syndrome in more than 50 children with HUS two years later [14]. As knowledge accumulated about the different nosologic entities presenting as HUS and the epidemiologic characteristics of the syndrome, we became aware that in our country, diarrhea accompanied the other symptoms in at least 90% of affected children. In 1981, we reviewed 95 children with HUS; gastrointestinal symptoms in the prodromic phase were present in 93% (unpublished data). We can speculate retrospectively that these patients’ disease probably was related to cytoxins of enterobacteria [15]. Thirty years later, we still have
no useful treatment, other than supportive measures, in this “classic” form of the syndrome [16–21].

Epidemiology

Let me begin by presenting an overview of the natural history of enteropathic, or diarrhea-associated, HUS. In the areas where HUS in children is endemic, the strong association with diarrhea prompted a search for an infectious agent in the stool. The sophisticated analysis by Chesney and Kaplan [22] on the patient discussed by Ullis and Rosenblatt [23] as having disseminated intravascular coagulation, and the epidemics of shigellosis complicated by HUS in Bangladesh [24] disclosed a close link between enterobacteria and HUS. In 1983, Karmali et al demonstrated a causal association between VTEC and HUS [25]. This finding was unequivocally confirmed two years later [26]. Between 1986 and 1989, three reports from Argentina suggested that the verotoxin-producing bacterium E. coli was the major cause of classic, epidemic HUS in this geographic area [27–29]. Lopez et al also showed that the E. coli serotype prevalent in other parts of the world, namely 0157:H7, was present in fewer than 5% of Argentine children with HUS, but that 48% of them had evidence of free fecal toxin; this finding strongly suggested the presence of different strains of the bacterium in Argentina [29]. On the other hand, the frequency of cytotoxin-associated gastroenteritis in Argentina is approximately 23%, much higher than the 0.6% to 2.4% in other parts of the world [30].

Clinical picture

The clinical picture of the acute phase of HUS in the three patients discussed today is typical of the epidemic form of the disease. For a few days preceding the sudden onset of pallor and central nervous system involvement, they all had diarrhea. Initial laboratory data showed a decreased hematocrit with fragmented erythrocytes in the peripheral blood smear and a low platelet count, characteristic of microangiopathic hemolytic anemia. The blood urea level was elevated, and all three patients were anuric on admission. The rest of the laboratory studies reflected alterations due to ARF. Diarrhea and vomiting are the most frequent of the prodromal signs and symptoms that occur in HUS. Figure 3 presents the prevalence of these prodromal signs and symptoms in 274 children admitted to two hospitals in Argentina whom we studied [31]. The acute stage of the disease was marked by hypertension, edema, hematologic abnormalities, and anuria; Figure 4 illustrates the prevalence of these and other findings in the acute stage [31]. The most frequent cause of ARF in Argentine children, HUS was diagnosed in 65% of 237 children admitted for ARF to our service. Another distinct feature of the acute form of HUS is the high incidence of neurologic involvement. Central nervous system (CNS) sequelae [3, 32–40] are infrequent. Hematologic changes occur only during the acute phase. The literature contains only occasional reports of persistent lesions in the liver [41], pancreas [42–45], colon [46], or other organs [38].

Fortunately, more than 95% of patients recover from the acute phase of the illness [31, 32]. The mortality rate is less than 5% (range, 0.5% to 4.5% between 1978 and 1993 in Argentina; data from the registry of the Nephrology Committee of the Argentine Society of Pediatrics).

The three patients presented today illustrate different courses of the renal lesion of the HUS. The first patient seems to have been cured after 13 years of followup. The second patient experienced a moderately severe acute stage and recovered from the ARF; his creatinine clearance (Ccr) eventually returned to normal. But he had persistent proteinuria and many years later developed hypertension, which then progressed to end-stage renal failure (ESRF). The third child had a very severe acute phase and arrived at ESRF without ever recovering acceptable renal function. She received a successful renal transplant.

After recovery from the ARF of HUS, renal function follows one of two patterns. In a few patients, the serum creatinine concentration does not totally return to the normal range, and ESRF develops relatively rapidly, an average of 4 years after the acute illness [47], as in Patient 3. We observed this course in 6 of 14 children who received renal transplants for HUS. In the second, more common pattern, the vast majority of patients recover normal renal function, at least as measured by Ccr or serum creatinine concentration. One year after the acute episode, one-half of them have a normal serum creatinine concentration and no proteinuria (by spot sample testing). In 6%, the Ccr is normal but proteinuria (rarely in the nephrotic range) is present. The remaining 45% have a reduced Ccr with proteinuria. Patients in the last two groups also can be hypertensive (Fig. 5). In our own study of patients after three years of followup, the proportion of patients with normal Ccr and no proteinuria increased to 62%; the group with normal Ccr but with proteinuria increased to 14%; and those with a diminished Ccr fell to 24%. Thus, some patients continue to recover from the acute insult even after the first year.
renal function deteriorated after a period of normal function. Pathogenesis

worse in patients with the atypical forms of HUS [7, 55, 56].

patients with HUS, one should select those with most patients of patients with a classic HUS following the same course (Table 2)

years thereafter; only few patients develop proteinuria after years of followup are highly likely to continue to do well for many years after onset of the acute disease [47]. Analysis of these children who are doing well after three

acute illness: among our 14 patients with HUS who received renal transplants, this slow course of progression was observed in 8 patients who began chronic dialysis as long as 22 years after their acute episode. We also have known of occasional patients with normal Ccr many years after the acute stage of their disease who, studying sequential pathologic specimens, established that the proportion of glomeruli involved in the acute insult was the same as the proportion of scarred glomeruli later [4]. Histologic changes in biopsy specimens from patients with chronic HUS [3, 64] show focal and segmental sclerosis and mesangial expansion in the glomeruli. These observations also suggest a hemodynamic mechanism as the cause of progressive scarring and progressive loss of renal function.

of followup [31]. Spizzirri et al reviewed patients from the same cohort followed for more than 10 years and found that 63% still had normal Ccr and no proteinuria; 18% had normal Ccr with persistent proteinuria; only 16% now had a reduced Ccr; and 3.4% were in ESRF (Fig. 5) [48]. One patient developed ESRF 20 years after the acute episode. We also have known of occasional patients who began chronic dialysis as long as 22 years after their acute illness: among our 14 patients with HUS who received renal transplants, this slow course of progression was observed in 8 children.

Studies from around the world have shown a similar proportion of patients with a classic HUS following the same course (Table 2) [3, 31, 48, 50—54]. We believe that in comparing outcomes in patients with HUS, one should select those with most patients having the diarrheal form of the disease. The outcome generally is worse in patients with the atypical forms of HUS [7, 55, 56].

Pathogenesis

Several years ago, we suggested that patients with HUS whose renal function deteriorated after a period of normal function

(measured by serum creatinine levels or Ccr) [57] did so because of hyperfiltration injury to the remaining nephrons [58, 59]. These patients almost always had associated proteinuria and also often had hypertension. Three lines of research have produced data compatible with that hypothesis. In our study [57], 4 of 12 patients with normal Ccr many years after the acute stage of their disease were unable to increase their inulin clearance when challenged with protein loads [60]. One possible interpretation of this finding is that these children are utilizing their "functional reserve" (prior to the protein load) in the presence of a reduced nephron mass [60]. Bosch’s recent review suggests that the best way to quantitate this diminished mass is determination of the maximal filtration capacity [61], namely, the maximum GFR achieved after a standardized protein load, and comparison of that determination with normal values for age. The mean peak inulin clearance after the protein load in the 12 HUS patients we studied was 84.9 ml/min/1.73 m², significantly lower than that in normal children (154.7 ml/min/1.73 m²) (P < 0.025) (Fig. 6) [57]. Not too surprisingly, the relation between creatinine clearance and inulin clearance was disproportionally high in some of the 12 children; tubular creatinine oversecretion probably maintained the normal serum creatinine levels.

The second line of research implicating hyperfiltration injury comes from Perelstein et al, who showed that some children who had completely normal clinical and laboratory findings years after an acute episode could develop microalbuminuria [62]. The authors speculated that increased filtration of albumin, implicated as the predictor of progressive lesions in other renal diseases [63], might cause the subsequent loss of renal function.

A third line of inquiry was reported by Habib and coworkers, who, studying sequential pathologic specimens, established that the proportion of glomeruli involved in the acute insult was the same as the proportion of scarred glomeruli later [4]. Histologic changes in biopsy specimens from patients with chronic HUS [3, 64] show focal and segmental sclerosis and mesangial expansion in the glomeruli. These observations also suggest a hemodynamic mechanism as the cause of progressive scarring and progressive loss of renal function.

Table 2. Long-term course of renal involvement in HUS

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>&quot;Normal&quot;a</th>
<th>Prot or HBP +</th>
<th>Ccr Followup years</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>50</td>
<td>56</td>
<td>10</td>
<td>2—5</td>
<td>54</td>
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<td>128</td>
<td>63</td>
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<td>118</td>
<td>63</td>
<td>18</td>
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<td>10—19</td>
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<tr>
<td>48</td>
<td>63</td>
<td>18</td>
<td>19</td>
<td>10—19</td>
</tr>
</tbody>
</table>

a Normal: no hypertension, no proteinuria, and normal creatinine clearance
b Prot: proteinuria; HBP: hypertension; Ccr: creatinine clearance

Fig. 5. Renal status at one, three, and >10 years of follow-up after the acute HUS [31, 48]. Hatched bar: normal Ccr, no proteinuria; vertical-striped bar: normal Ccr, proteinuria; open bar: decreased Ccr, proteinuria.

Fig. 6. Mean CIN before and 2 hrs after a protein load in HUS patients at follow-up. Cross-hatched bar: HUS; horizontal-hatched bars: controls.
Many studies have searched for findings in the acute stage of HUS that would precisely predict the late course of the illness. The presence of diarrhea and the characteristics of classic, epidemic HUS are associated with a better prognosis; the variables predicting a poor prognosis are those associated with the initial destruction of a larger number of nephrons. Not too surprisingly, the presence of anuria and its duration as well as the need for, and duration of, dialysis are the variables commonly reported to predict late outcome [48-54]. As I mentioned earlier, studies of the pathologic features in the acute phase have shown that the percentage of compromised glomeruli can predict the late course [4, 50]. Persistent hypertension also increases the risk for chronic sequelae [3, 31, 48-54]. Severe extrarenal manifestations [65], such as marked CNS symptoms [51, 54] and bloody diarrhea or rectal prolapse [66], also are associated with a poor long-term outlook. These signs probably simply reflect a more severe disseminated microangiopathic process. Recently, Renaud and coworkers concluded that age at onset, long considered of prognostic significance, is not. They demonstrated that the difference in outcome between infants and older children is simply due to the higher frequency of the atypical subset of HUS (with its known poorer outcome) in older children [57].

Management of chronic renal disease following acute HUS

Children who have normal creatinine clearance but persistent proteinuria one year after an acute episode of HUS are at risk of developing progressive renal failure [31, 48]. Persistent hypertension also is a predictor of a poor outcome. However, even patients with a normal Ccr, no proteinuria, and normal blood pressure can develop progressive renal insufficiency. Our approach is to start treatment if the patient has persistent proteinuria of any degree one year after the acute episode. First, we limit the protein in the diet to the recommended dietary allowance [67]; most middle class children in our country consume amounts exceeding it. Next, we try to reduce blood pressure to average or low-normal values with ACE inhibitors. Third, even if the patient has normal blood pressure, we administer angiotensin-converting-enzyme (ACE) blockers. Although there is no conclusive evidence that this treatment program prevents the progression of HUS, studies in experimental animals [68, 69] and in other human renal diseases in which a similar mechanism might be present [70-72] have demonstrated a reduction in proteinuria and a diminution in the rate of functional deterioration. Briones and colleagues from the Pediatric Hospital of Buenos Aires have reported in abstract that administration of ACE inhibitors decreased proteinuria from 63.5 ± 11.2 mg/m²/hr to 9.8 ± 2.0 mg/m²/hr in 25 children with renal sequelae post HUS [73]. A long-term, prospective multicenter study of a larger number of patients will be needed to provide definitive conclusions regarding the efficacy of a low-protein diet or ACE inhibition in patients with renal sequelae following HUS.

Hemolytic-uremic syndrome accounts for about 20% of children who enter ESRF programs in Argentina [74]. Since the report from Cerilli et al in 1972 [75], renal transplantation has become a routine treatment for children with HUS who progress to ESRF. Although scattered case reports describe recurrence of HUS in the graft [9, 76-82], several groups have found no recurrence of HUS in a substantial number of patients [47, 83-87]. In addition, Gagnadoux and colleagues, although not observing recurrences in the epidemic form, reported that patients who received renal grafts because of HUS had a worse long-term prognosis than did children whose original renal disease was not HUS [86].

Three problems complicate an analysis of the risk of recurrence of HUS in a transplanted kidney: (1) Thrombotic microangiopathy can be the pathologic pattern of acute immunologic rejection [79]. (2) Thrombotic microangiopathy has been seen in renal allografts in patients receiving cyclosporine whose original disease was not HUS [88-90] and in patients with bone marrow [91, 92] or liver transplantation [93]. (3) Recurrence has been reported predominantly in older children and in adults, and in patients who had recurrent or non-epidemic familial types of HUS [9, 76-81].

When we first reviewed our own experience with transplantation in children with HUS, we found that the only patient who had a recurrence that led to the loss of his graft (two months post transplantation) was an 8-year-old boy who had had a severe, acute HUS not preceded by gastrointestinal symptoms. He did not recover from the acute failure and required hemodialysis until transplantation. His brother had had non-diarrheal HUS, equally severe, 5 years previously [47]. Since then, we have transplanted kidneys into 4 other children with atypical HUS, and we have not observed another recurrence. More recently, we reviewed the course of 23 renal transplants in 20 children whose original disease had been HUS [94]. Hemolytic-uremic syndrome had been preceded by diarrhea in 16 patients who had presented with the classic epidemic type; this group received 19 grafts. The survival of these 19 grafts, maintenance of stable renal function, incidence of acute rejection, and prevalence of proteinuria and hypertension were compared with the same measures in a randomly selected group of 19 children who received renal transplants because of ESRF not due to HUS (“controls”). Mean followup in both groups was 5 years, with a range of 1 to 11 years. Actuarial survival of the grafts (in patients with or without preceding HUS) and of the grafts with normal serum creatinine was similar in the two groups (P = 0.73 and 0.27, respectively, log-rank test) (Figs. 7, 8). Mean survival of the grafts was 7.16 years in the HUS patients versus 8.53 years in the controls (P, NS). Mean survival with a normal serum creatinine was 2.07 (HUS) versus 2.71 years (controls) (P, NS). There were 14 acute rejections in the HUS patients versus 8 episodes in the control group (P, NS). Prevalence of proteinuria and hypertension at 1 and 5 years post transplantation was similar for the two groups. No evidence of thrombotic microangiopathy was seen in the 6 transplanted kidneys surgically removed or in the 6 biopsies performed for other diagnostic purposes. We conclude that patients who receive renal transplants for classic epidemic HUS have a very low risk of disease recurrence and that the long-term outcome of the grafts in these patients is not different from that in patients with ESRF from other causes. Moreover, in patients whose original disease was classic HUS, the use of cyclosporine A in 12 of the 19 grafts did not seem to increase the risk of recurrence.

1 One has to be cautious in reducing dietary protein, since you can cause other essential components (calcium, zinc, iron) to fall below their recommended dietary allowances [67].
Conclusion

In the classic, epidemic form of HUS in children, mortality in the acute stage now is lower than 5%. Children usually die due to intercurrent infection or severe neurologic, intestinal, or myocardial complications associated with the more severe patterns of the acute disease. Treatment in the acute phase is supportive. With modern methods of management of fluid and electrolyte disorders and of hypertension, no patient should die of the complications of ARF. Of the 95% who survive, approximately one-third are at risk of having chronic sequelae. The chronic course is characterized predominantly by the hemodynamic sequelae of the renal lesion produced during the acute stage. Motor, sensory, or intellectual deficits; diabetes; myocardial infarctions; or intestinal strictures are infrequent. We believe that enough evidence supports the hypothesis that the progressive renal failure of HUS is due to the glomerular and tubulo-interstitial scarring related to the initial decrease of the nephron mass by the acute microangiopathic process, and not to persistence or recurrence of the original disease.

Three courses of progression to ESRF have been described. Children with the most severe forms do not recover from the ARF and enter directly into a dialysis and transplantation program. A second group recovers renal function partially but with persistent proteinuria and hypertension; subsequent progression to ESRF occurs in two to five years. The third group, the majority of those who progress to renal failure, ultimately initially recover normal serum creatinine and creatinine clearance levels; some of these patients do, however, develop proteinuria and/or hypertension. These children progress to ESRF after more than five years, at times as late as 20 years after the acute disease. Treatment in the later years seeks to prevent the progression of chronic renal insufficiency. Transplantation is indicated in this form of HUS, as there is little, if any, risk of recurrence, and the prognosis is similar to that of patients who receive renal transplants for other diseases.

Questions and Answers

Dr. John T. Harrington (Dean, Tufts University School of Medicine, Boston, Massachusetts, USA): Dr. Repetto, you said that few patients over the age of three develop “classic” HUS. What accounts for this immunity in children older than three? Do we know what specific antibodies are responsible?

Dr. Repetto: This is a very interesting question. I know of no data based on specific studies to answer it, but one can speculate. In Argentina, these children appear to be in contact with the verotoxin in the second half of the first year of age, when most of them stop being breast-fed and start incorporating meat and unpasteurized milk into their diet. Due the high prevalence of VTEC in our country, susceptible children would develop HUS then. There seems to be some kind of immunity either to the VTEC or to the toxin; there have been no reports of well-documented recurrences in this type of HUS, although no specific immunity has been found. Children over three years could have the same kind of protection if they are among those who had VTEC infection without developing HUS. In the group studied by Lopez et al, 19% of children with diarrhea not developing HUS had either VTEC in the stools, production of verotoxin from the stool culture, or serum antibodies against verotoxin [29, 30]. The possibility also exists that verotoxin receptors are differently expressed at different ages. We have seen patients who developed HUS shortly after their arrival from other countries. Some of their older siblings presented bloody diarrhea, but we could not find any laboratory evidence of even subclinical HUS.

Dr. Manuel Martinez-Maldonado (Professor and Vice-Chair, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA): Have any attempts been made to biopsy the kidneys of the patients in whom proteinuria, hypertension, or both occur one year or more after acute HUS? If so, what lesion is found? Thrombotic microangiopathy is mostly part of the acute response. If later lesions are also thrombotic microangiopathy, are
these re-exposure to toxin from shiga-like E. coli 0157:H7 or “memory of cells” to other stimuli?

**DR. REPETTO:** Habib et al reported the histologic findings in sequential biopsies obtained during the acute period and one year later [4]. When they correlated the clinical data with the late biopsy results, they found that the patients who had hypertension, proteinuria, and/or any decrease of creatinine clearance showed the typical findings associated with the chronic renal sequelae, namely, expansion of the mesangium, increased mesangial cellularity, interstitial infiltrates, tubular atrophy, and focal glomerular sclerosis. This has also been the experience of Gallo and his team [3, 64].

**DR. MARTINEZ-MALDONADO:** Was thrombotic microangiopathy present in the followup?

**DR. REPETTO:** No. Dr. Habib was very careful in looking for that feature, and she could not find any sign of acute thrombotic microangiopathy.

**DR. MARTINEZ-MALDONADO:** Let me return to Dr. Harrington’s question. In Argentina, if lesions of thrombotic microangiopathy presented later, it could mean one of two things: either a re-exposure to the verotoxin or “memory” of the kidney in its response to other stimuli, but the response is the same. I wonder what you think about that.

**DR. REPETTO:** We have never seen recurrences of HUS in children who present with the typical epidemic form. Nor have I recalled this fact in my talks with other pediatric nephrologists in Argentina. The lack of recurrences probably is due to some kind of immunity against the VTEC prevalent in our country or to the toxin, but I don’t think that this has anything to do with the kidney itself. We usually tell the parents of these children, if we are sure that we are dealing with the epidemic diarrheael form, that with our experience gathered over four decades, the disease is highly unlikely to recur. Patients who do develop recurrences clearly have atypical forms of HUS, and most of them have more than one recurrence, at times associated with hypocomplementemia [55].

**DR. NICOLAOS E. MADIAS** (Chief, Division of Nephrology, New England Medical Center, Boston): First, I would like to make a comment. Regarding the increased susceptibility of young children to epidemic HUS, the shiga-toxin receptor is now well characterized. It would be of interest to look for different expression of the receptor in young children versus older age groups. It is possible that this could differ as a function of age.

My question relates to your comment that only supportive care is indicated in patients with epidemic HUS. Although so-called atypical HUS clearly has a worse outcome, epidemic HUS does not strike me as a benign disorder, given that as many as 5% of the affected children die in the acute phase, about 5% develop CNS sequelae, some children never recover from ARF, and about 40% develop long-term renal abnormalities. How vigorously have therapies such as plasma infusion or exchange been studied in this disorder? One might make the case for using these approaches in the children who present with the most serious clinical characteristics.

**DR. REPETTO:** Regarding your comment, I believe that the studies of receptors comprise a new avenue for research that could yield important knowledge for the management of HUS. Now, let me answer your question. Numerous studies have reported results of treatment in the acute phase [16–21], testing inhibitors of platelet aggregation, anticoagulants, or high-dose intravenous gamma globulin. Unfortunately, results generally have been discouraging. Three carefully designed studies in populations in which most children had the diarrheal form were prospective and controlled. One was performed by Drs. Vitacco and coworkers in Buenos Aires many years ago [17]. At that time, because intravascular coagulation was believed to be responsible for HUS, some groups advocated the use of heparin. These authors studied children with the most severe forms of epidemic HUS, comparing heparin versus conventional treatment in a randomly selected control group. Not only they did not find any benefit of heparin treatment, but they noticed an increased risk of intracranial hemorrhage. Two other more recent, multicentric, prospective, and controlled studies came from Italy and France [20, 95]. Because plasma infusion or plasmapheresis had been reported as effective in the control of the acute phase of the atypical forms of HUS—possibly because of the altered metabolism of the vascular endothelial products that prevent the microthrombosis—these investigators studied a total of 56 children, about 80% of whom had associated gastroenteritis. Patients treated with plasma infusion for two to three weeks had no better outcome than did those control patients treated supportively, both in the acute phase and during a mean followup of 16 and 12 months. My own belief is that epidemic HUS is a one-shot disease and that by the time the patients get to us, the thrombotic microangiopathy is already established. I believe that all efforts should be directed towards preventing intestinal infection or the effect of the verotoxin.

**DR. LUIS SALINAS-MADRIGAL** (Professor of Pathology, Internal Medicine and Pediatrics, St. Louis University Cell Sciences Center, St. Louis, Missouri, USA): Horacio, I was very much interested in the fact that cyclosporine does not influence the incidence of recurrence of the disease in the epidemic form. We have transplanted kidneys into three adults with idiopathic HUS and one patient with mitomycin-induced HUS. In those four patients, cyclosporine seemingly produced early recurrence of the thrombotic process in the graft. Does this mean that we are talking about different entities when we discuss the idiopathic versus the epidemic form? Might this explain many of the differences in the response to treatment? You just mentioned plasma infusion as being more effective in the idiopathic forms as compared with the epidemic form; this is a fascinating difference, I think.

**DR. REPETTO:** We have transplanted kidneys into five children with the atypical form of HUS. One had the recurrence that I related in my discussion. The other four received triple therapy with lower doses of cyclosporine, yet we have not seen either a hematologic or a renal recurrence. The experience in other centers in our country [87] and in France [86] with transplantation in the epidemic enteropathic form is the same. Cyclosporine does not seem to add to the risk of recurrence. But, as you just heard, I still think that the analysis of its responsibility in recurrences is quite difficult. We are aware of the effect of cyclosporine on the endothelium and the mesangium, but its direct participation in recurrences of HUS has yet to be proven. On the other hand, as I said, I am convinced that we are talking of different pathogenetic entities that produce the same clinical syndrome and pathologic lesion. The nosologic problem is further increased by the fact that evidence of verotoxin infection has been demonstrated in children with HUS who did not present with diarrhea.
Family members of children with diarrheal HUS [96].

Infections exist in the parents or siblings of affected patients?

Growing period, that is, until they are about 20 years of age.

Outcome. This is why I follow these children until the end of their

Who appear cured after more than three years of followup. We

Aires School of Medicine, Buenos Aires): We think that the best predictor

for CRF [98]?

Diagnosis of ESRD, or at least slow it down, but we need more data to

Confirm this conjecture.

What is the VTEC type in this country?

DR. REPETTO: Yes, we start reducing the protein load and giving

them ACE inhibitors when proteinuria persists one year after the

acute event. We think that we might be able to prevent progress-

ion of ESRD, or at least slow it down, but we need more data to

confirm this conjecture.

DR. ARRIZURIETA: What is the VTEC type in this country?

DR. REPETTO: Lopez and coworkers showed that 0157:H7 E.

coli was only 2% of the verotoxin-producing E. coli isolated [29];

prevalence in other parts of the world ranges between 40% and

79%. There are sporadic reports of 011, 025:H2 etc. from our

country [96]. Both groups are conducting studies to gather more

information.

DR. JORGE FERRARIS (Chief of Pediatric Renal Transplantation,

Hospital Italiano, Buenos Aires): We think that the best predictor

of CRF is the length of the acute phase. For example, a patient

with a severe acute phase, more than 14 days of oligoanuria, has a

90% chance of developing CRF; a patient with a moderate acute

phase, 7 to 14 days of oligoanuria, has a 30% chance; and a patient

with a mild acute phase, less than 7 days of oligoanuria, has less

than a 2% chance of developing CRF [97]. My question is, what do

you think about using leukocytosis in the acute phase as a

predictor of CRF [98]?

DR. REPETTO: We have not looked at that specifically. British

groups have postulated that the leukocyte elastase is a putative

intermediate in triggering the lesion [99-101], but I cannot answer

the question based on our own experience.

DR. FERRARIS: How long should the followup be in patients with

mild HUS?

DR. REPETTO: This question reveals part of a big dilemma in

following these children. The predictive correlations you men-

tioned are, of course, statistical, and we have had patients with

only 1 or 2 days of anuria who ended up in CRF. On the other

hand, we have seen infants with anuria lasting more than 10 days

who appear cured after more than three years of followup.

We have to establish more exact methods for predicting the final

outcome. This is why I follow these children until the end of their

growing period, that is, until they are about 20 years of age.

DR. RAMON EXENI (Chief, Department of Nephrology, San Justo

Children’s Hospital, Province of Buenos Aires): Do verotoxin

infections exist in the parents or siblings of affected patients?

DR. REPETTO: Studies have looked for familial contagion of the

VTEC [102]. In our country, a very recent publication reported

cumulative evidence of VTEC infection in more than 30% of

family members of children with diarrheal HUS [96].
with acute diarrhea. Two studies have shown an increased risk of
mention that antimotility agents are contraindicated in children
in Holland are proceeding (personal communications).
reporting of cases occurring in nursing homes or day-care centers
drinking milk obtained directly from cows [119]. I also believe that
that a high proportion of their patients develop HUS as a result of
[118]. A group from La Plata, Province of Buenos Aires, reported
public awareness should reduce the risk of consuming under-
HUS. One is the public health area. Adequate counseling and
prompted any dietary measures or vaccines for preventing the
ACE inhibitors and reducing the dietary protein load.
know what is going to happen now that we are routinely using
not aggressively treat patients in the chronic stage. We still don’t
remaining nephrons are hyperfunctioning in this clinical model. If
you are very critical, you might not decide to start treatment at
the stage of microalbuminuria.
Dr. Repetto: I could agree with you, and we are thinking of
doing that. The problem is that no one has yet verified that the
remaining nephrons are hyperfunctioning in this clinical model. If
you are very critical, you might not decide to start treatment at
that early stage. I believe that a prospective research study should
be developed before implementing this approach as routine
treatment. Let me point out that the results showing the propor-
tion of patients arriving at ESRF came from a time when we did
not aggressively treat patients in the chronic stage. We still don’t
know what is going to happen now that we are routinely using
ACE inhibitors and reducing the dietary protein load.
Dr. Rodolfo S. Martin (Career Investigator, Institute of Med-
ical Research, University of Buenos Aires School of Medicine): Has
our new knowledge gained about shiga-like toxins (verotoxotoxin)
prompted any dietary measures or vaccines for preventing the
syndrome?
Dr. Repetto: Yes, three areas promise hope for preventing
HUS. One is the public health area. Adequate counseling and
public awareness should reduce the risk of consuming under-
cooked meat [116], unpasteurized cheese [117], and raw milk
[118]. A group from La Plata, Province of Buenos Aires, reported
that a high proportion of their patients develop HUS as a result of
drinking milk obtained directly from cows [119]. I also believe that
reporting of cases occurring in nursing homes or day-care centers
should be mandatory [118].
A second approach is, as you mentioned, vaccines. I believe that
we do not have the necessary pharmacologic infrastructure to
develop them in our country. Fortunately, efforts in Canada and
in Holland are proceeding (personal communications).
The third approach, as I mentioned in my answer to Dr. Exeni, is the use of orally administered toxin-binding resins. I should
mention that antimotility agents are contraindicated in children
with acute diarrhea. Two studies have shown an increased risk of
HUS and increased severity of neurologic manifestations with
their use [36, 120].

Reprint requests to Dr. H. Repetto, T. García 2369, 1426, Buenos Aires, Argentina

NOTE ADDED IN PROOF
A significantly increased number of neutrophils within the glomeruli of
D+ HUS was reported in a recent multicentric pathology study in
England.

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TAYLOR CM ON BEHALF OF THE BRITISH ASSOCIATION FOR PEDIATRIC
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