Early Volume Expansion and Outcomes of Hemolytic Uremic Syndrome

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BACKGROUND: Hemolytic uremic syndrome associated with Shiga toxin–producing Escherichia coli (STEC-HUS) is a severe acute illness without specific treatment except supportive care; fluid management is concentrated on preventing fluid overload for patients, who are often oligoanuric. Hemoconcentration at onset is associated with more severe disease, but the benefits of volume expansion after hemolytic uremic syndrome (HUS) onset have not been explored.

METHODS: All the children with STEC-HUS referred to our center between 2012 and 2014 received intravenous infusion targeted at inducing an early volume expansion (+10% of working weight) to restore circulating volume and reduce ischemic or hypoxic tissue damage. The short- and long-term outcomes of these patients were compared with those of 38 historical patients referred to our center during the years immediately before, when fluid intake was routinely restricted.

RESULTS: Patients undergoing fluid infusion soon after diagnosis showed a mean increase in body weight of 12.5% (vs 0%), had significantly better short-term outcomes with a lower rate of central nervous system involvement (7.9% vs 23.7%, \( P = .06 \)), had less need for renal replacement therapy (26.3% vs 57.9%, \( P = .01 \)) or intensive care support (2.0 vs. 8.5 days, \( P = .02 \)), and needed fewer days of hospitalization (9.0 vs 12.0 days, \( P = .03 \)). Long-term outcomes were also significantly better in terms of renal and extrarenal sequelae (13.2% vs 39.5%, \( P = .01 \)).

CONCLUSIONS: Patients with STEC-HUS had great benefit from early volume expansion. It is speculated that early and generous fluid infusions can reduce thrombus formation and ischemic organ damage, thus having positive effects on both short- and long-term disease outcomes.

WHAT'S KNOWN ON THIS SUBJECT: Shiga toxin–producing Escherichia coli, for which there is no specific treatment, is always associated with oligoanuric acute kidney injury, and its management is concentrated on preventing fluid overload by means of fluid restriction or dialysis.

WHAT THIS STUDY ADDS: Early and generous volume expansion in Shiga toxin–producing Escherichia coli improves all short- and long-term disease outcome indicators.

Dr Ardissino conceptualized and designed the study, analyzed the data, and drafted the initial manuscript; Dr Tel performed data collection and edited and revised the manuscript; Dr Possenti designed the data collection instruments, performed data collection, and revised the manuscript; Dr Testa designed the data collection instruments and revised the manuscript; Dr Consonni performed the statistical analysis and revised the manuscript; Drs Pagliaroni, Salice, and Monzani performed data collection and revised the manuscript; Ms Salardi, Ms Daprai, and Drs Borsa-Ghiringhelli, Tedeschi, Castorina, Colombo, Arghittu, Tozzoli, and Brigotti performed laboratory assessment and revised the manuscript; Ms Torresani conceptualized and designed the study and revised the manuscript; and all authors approved the final manuscript as submitted.
Hemolytic uremic syndrome (HUS) is the most common cause of pediatric acute kidney injury (AKI) and one of the most serious acute diseases affecting children in Western countries, with a case fatality rate of 3% to 5% and a 5% to 10% risk of significant sequelae. The disease is not limited to children, as it clearly appeared in the outbreak of Shiga toxin (Stx)–producing Escherichia coli (STEC) infection occurred in Germany (2011), which caused >800 adult cases. HUS is defined as the simultaneous occurrence of platelet consumption, microangiopathic hemolysis, and acute organ injury. In ~85% of cases, the disease develops as a complication of STEC intestinal infection.

The most commonly involved organs are the kidneys, but thrombotic microangiopathy (TMA) can also affect the liver, brain, heart, pancreas, and skin. Death is usually related to central nervous system (CNS) involvement, which is observed in 17% to 52% of cases. STEC-HUS still has no specific treatment, so children can only be given supportive care: transfusions, correction of acidosis and electrolyte abnormalities, antihypertensive treatment, nutrition, and renal replacement therapy (RRT) for fluid removal and metabolic abnormalities. The rate of dialysis during the acute phase of STEC-HUS varies widely, from 47% to 70%, and the use of antibiotics is still controversial.

Given the parenchymal nature of the renal injury and the associated oligoanuria, the care of patients with HUS has been greatly influenced by the risk of fluid overload (FO) and medical intervention has therefore been classically characterized by fluid restriction and removal (dialysis). However, recent studies have demonstrated that hemoconcentration and dehydration, which often coexist at HUS onset, are risk factors for more severe hematologic, renal, and neurologic involvement and also negatively affect long-term disease outcomes.

The aim of this study was to investigate whether early volume expansion (VE) can reduce the severity of HUS on the grounds that fluid infusion (FI) may limit the intravascular volume depletion, thus reducing thrombus formation and organ hypoperfusion and the consequent hypoxic and ischemic damage.

METHODS

A network of 56 pediatric units has been operating in northern Italy since May 28, 2010 with the aim of centrally diagnosing STEC infections and STEC-HUS early, by screening cases of bloody diarrhea for the presence of Stx genes (1 and 2) in the feces by using a reverse dot blot commercial kit, as described in detail elsewhere. Since January 1, 2012, given our increasing awareness of the potential role of hemoconcentration and dehydration in conditioning the severity of the disease and to expand intravascular volume, all the patients with HUS involved in this program routinely received infusions of saline solution from the time of the diagnosis of HUS until reaching their target weight, defined as +7% of working weight (WW) if plasma albumin is >3 g/dL or +10% of WW if plasma albumin is <3 g/dL. WW was determined on the basis of the patients’ historical weight as reported by their parents and on clinical evidence. All cases started the infusion protocol the very same day of HUS diagnosis (often before referral to our center) with 10 to 15 mL/kg per hour (depending on the severity of dehydration) of 0.9% saline solution. After few hours, once all laboratory results were available and the clinical conditions were more clear, the solution was regularly changed in dextrose (5%) solution with NaCl 130 mEq/L. Once the target weight was reached, the infusion was reduced and continued to maintain the target weight.

To avoid dangerous FO, patients’ body weight was strictly monitored every 12 hours. Stroke volume was occasionally estimated and used as a surrogate marker of circulating volume, and both target weight and infusion were adjusted accordingly.

We reviewed the records of all children with a diagnosis of STEC-HUS referred to our center between January 2012 and December 2014 (group B) to collect detailed information on age, weight, blood pressure, heart rate, serum urea, creatinine (sCr), lactate dehydrogenase (LDH), uric acid, plasma albumin and hemoglobin levels, and platelet count; the length of hospitalization, treatment in PICU, and RRT; significant neurologic events (seizure, coma, confusion, pyramidal or extrapyramidal syndromes) and other complications during the acute phase (including death); and systemic and renal sequelae. Renal sequelae were categorized as major, chronic kidney disease (CKD) stage 2 to 5 (eGFR <90 mL/min/1.73 m²), or minor, CKD stage 1 (defined as abnormal proteinuria or microalbuminuria or hypertension with an eGFR of ≥90 mL/min/1.73 m²). The Schwartz formula was used to calculate the eGFR. Renal long-term sequelae were all based on a minimum follow-up of 12 months after the acute disease.

In the presence of active TMA (platelet consumption, hemolysis, and renal damage), the diagnosis of STEC-HUS was based on the detection of free fecal Stx S and/or STEC isolation and/or the detection of serum antilipopolysaccharide antibodies against the STEC serotypes most commonly associated with HUS: O26, O157, O103, O111, and O145.

Patients with atypical HUS (eg, familial, recurrent, associated with other specific causes...
such as complement dysregulation, methylmalonic acidemia, AIDS, pneumococcal infection, drugs), were excluded. The very few patients with diarrhea followed by HUS who were negative for Stx in the stools and for antilipopolsaccharide antibodies against the “top 5” STEC serotypes were screened for genetic complement dysregulation.

In our center, RRT for STEC HUS is generally considered when patients are anuric and have a urea level of >250 mg/dL or significant intravascular FO.

The clinical and laboratory parameters indicating the course of the disease were compared with those of an equal number of historical sequential (unselected) patients referred to our center in the period 2006 to 2009 (group A), when patients were not actively infused or fluid intake was frankly restricted. Patients admitted in 2010 and 2011 could not serve as controls because during that specific period the policy of fluid management at our center was changing, with some patients simply not restricted or timidly infused, leading to an equivocal management approach.

The Ethics Committee of our hospital was informed about the study, which was conducted in accordance with our institution’s ethical regulations.

**Statistical Analyses**

The data are expressed as mean values ± SD or median values and the 25th and 75th centiles (interquartile range [IQR]).

Student’s t test and χ^2^ test were used for comparing the continuous and categorical variable, respectively, between the 2 treatment groups. In case of non-normality (platelet, sCr, urea, LDH), continuous variables were log-transformed before tests were performed.

To compare the risk of selected categorical outcomes in group A versus group B, we calculated univariate risk ratios (RRs) and 95% confidence intervals (CIs). When the RR was not quantifiable (because of 0 outcomes) or when there were <5 outcomes in the 2 groups combined, Fisher’s exact test was used.

To compare length of stay in hospital in group A versus group B, the geometric mean ratio was calculated.

To calculate risks of any categorical outcome in relation to hemoglobin levels, we fitted 2 univariate logistic regression models to calculate the odds ratios (OR) per milligram per deciliter of hemoglobin in groups A and B, respectively. Then we calculated the predicted risks (P) in each treatment group using the formula $P = \text{odds}/(1 + \text{odds})$.

Analyses were performed with Stata 13 (Stata Corp, College Station, TX).

**RESULTS**

The control group (group A) and the group of patients treated with VE (group B) consisted of 38 subjects each. There were no significant between-group differences in gender distribution, age, weight, days of illness before HUS diagnosis, blood pressure, white blood count, hemoglobin, albumin and uric acid levels, or platelet counts (Table 1) at the time of diagnosis, and mean sCr and LDH levels were significantly lower in group B, proving their earlier diagnosis compared with controls.

All patients in group B were initially actively infused regardless of their urine output, in accordance with the study methods, and as expected the infusion led to a significant increase in body weight early in the course of the disease, with a mean weight gain of 1.65 ± 1.43 kg (+12.5%) after 48 hours. The patients in group A had fairly stable body weight because of the strict limitation of fluid intake or active fluid removal by means of dialysis (Fig 1).

**Laboratory Evaluation**

The trends of the TMA-related clinical and laboratory parameters during the 96 hours after diagnosis of HUS are shown in Table 2. There was a clear and clinically relevant increase in sCr, urea, LDH, and uric acid concentration in group A (with the highest median value reached after 24–48 hours), whereas group B showed either a progressive and regular decline (uric acid) or a stable level of the parameters (LDH, sCr, urea). In particular, urea level (most

<table>
<thead>
<tr>
<th>TABLE 1 Comparison of Clinical and Laboratory Characteristics (Median and IQR) at HUS Diagnosis of Patients Addressed to Early FI (Group B) and Controls (Group A)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No.</strong></td>
</tr>
<tr>
<td>Gender (M/F)</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Wt (kg)</td>
</tr>
<tr>
<td>Days of illness (before the HUS diagnosis)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Systolic</td>
</tr>
<tr>
<td>Diastolic</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
</tr>
<tr>
<td>sCr (mg/dL)</td>
</tr>
<tr>
<td>White blood count (x10^9/L)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
</tr>
<tr>
<td>PTL (x10^3)</td>
</tr>
<tr>
<td>Serum LDH (UI/mL)</td>
</tr>
<tr>
<td>Plasma albumin</td>
</tr>
<tr>
<td>Serum uric acid</td>
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</tbody>
</table>

Hb, hemoglobin; PTL, platelet count.
relevant for dialysis indication) reached a statistically significant difference at 24 and 48 hours, with group A higher than B (Table 2). No between-group differences in systolic or diastolic blood pressure were observed.

The median peak levels (and IQR) of all TMA-related laboratory parameters (Fig 2) were significantly higher in group A: sCr 5.06 (1.74–6.57) vs 2.31 (0.84–4.18) mg/dL (P = .03), urea 210.5 (128–251) vs 141.5 (99–224) mg/dL (P = .05), and LDH 5631 (2840–7260) vs 3652 (1774–4505) IU/L (P = .02). Median nadir platelet counts were significantly lower in group B than in group A: 50.5 (23–68) × 10^3/mm^3 vs 25.0 (17–58) × 10^3/mm^3 (P = .04).

**Outcome Evaluation**

The patients in group A needed RRT significantly more often than those in group B (57.9% vs 26.3%; RR 0.45; P = .01) (Table 3), without any difference in the number of days on RRT before renal function recovered: 4 (2.5–11.5) in group A and 3 (2.75–11.5) in group B (P = .84). The mean peak sCr and urea levels of patients who underwent RRT and those who did not in group A and B were not different (Fig 3).

Clinically evident CNS involvement was not statistically different (P = .06), and the number of days spent in PICU and in the hospital revealed a significantly better outcome in patients actively infused compared with controls. The same holds true for the long-term sequelae (Table 3).

Two of the patients in group A died early from CNS involvement, and 1 suffered severe and irreversible visual impairment and progressive CKD; none of the patients in group B died, but 1 developed insulin-dependent diabetes mellitus.

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**TABLE 2** Comparison of Clinical and Laboratory Characteristics (Median and IQR) During the First 4 d After HUS Diagnosis of Controls and of Patients Addressed to Early FI

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt (kg)</td>
<td>A</td>
<td>17.0 (12.4–19.2)</td>
<td>17.6 (12.7–20.5)</td>
<td>17.0 (12.5–19.4)</td>
<td>17.3 (12.4–20.1)</td>
<td>17.3 (12.3–19.8)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>14.4 (11.1–23.7)</td>
<td>16.1 (12.5–24.9)</td>
<td>16.2 (12.8–25.3)</td>
<td>15.8 (12.1–26.2)</td>
<td>15.8 (12.2–26.4)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>A</td>
<td>110 (100–122)</td>
<td>105 (95–119)</td>
<td>105 (99–115)</td>
<td>110 (100–119)</td>
<td>110 (101–129)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>A</td>
<td>70 (60–78)</td>
<td>65 (54–77)</td>
<td>61 (58–68)</td>
<td>68 (61–76)</td>
<td>70 (57–77)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>69 (60–74)</td>
<td>68 (60–75)</td>
<td>68 (64–74)</td>
<td>69 (59–75)</td>
<td>68 (58–75)</td>
</tr>
<tr>
<td>PTL (x10^3/mm^3)</td>
<td>A</td>
<td>67 (42–110)</td>
<td>59 (36–78)</td>
<td>67 (49–94)</td>
<td>78 (38–112)</td>
<td>102 (53–130)</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>A</td>
<td>3756 (1722–5192)</td>
<td>4164 (2480–5352)</td>
<td>5256 (2895–5898)</td>
<td>3988 (2156–5831)</td>
<td>3854 (2316–6382)</td>
</tr>
<tr>
<td>sCr (mg/dL)</td>
<td>A</td>
<td>2.0 (1.1–3.3)</td>
<td>2.5 (1.5–4.1)</td>
<td>3.5 (1.4–4.5)</td>
<td>3.4 (1.2–5.3)</td>
<td>3.5 (1.2–4.2)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.4* (0.7–2.1)</td>
<td>1.5* (0.7–2.5)</td>
<td>1.3* (0.6–3)</td>
<td>1.5* (0.5–3.4)</td>
<td>1.2 (0.5–3.7)</td>
</tr>
<tr>
<td>Ser. urea (mg/dL)</td>
<td>A</td>
<td>122 (78–203)</td>
<td>155 (105–198)</td>
<td>161 (122–203)</td>
<td>137 (114–212)</td>
<td>127 (92–168)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>105 (56–142)</td>
<td>107* (86–135)</td>
<td>111* (57–172)</td>
<td>106 (38–167)</td>
<td>90 (38–182)</td>
</tr>
<tr>
<td>Ser. uric acid (mg/dL)</td>
<td>A</td>
<td>8.7 (6.7–11.1)</td>
<td>10.7 (8.1–11.5)</td>
<td>9.8 (7.9–12)</td>
<td>9.3 (7.4–11.9)</td>
<td>7.5 (6.1–9.5)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>8.6 (6.3–9.8)</td>
<td>8.3* (6.5–9.3)</td>
<td>7.8* (5–9.4)</td>
<td>6.7 (5–10.6)</td>
<td>6.8 (4.9–10.5)</td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; PTL, platelet count; SBP, systolic blood pressure. * P < .05 versus Group A.
To exclude the possibility of milder cases being overrepresented in group B, we performed an additional analysis restricted to the most severe cases (sCr >2 mg/dL at baseline) of both groups A and B. Even in this setting, the better outcome in group B (n = 12) compared with group A (n = 20) was clearly confirmed as to the need for RRT (41.7% vs 70.0%; P = .11), involvement of the CNS (8% vs 29%; P = .39), and long-term sequelae (13.8% vs 37.8%; P < .03).

The predicted risk of combined short- and long-term complications in group A showed a strong association with baseline hemoglobin level (OR 1.57 per g/dL; 95% CI, 1.10–2.24; P = .01) (Fig 4A). In group B, the active infusion led to a substantially weaker relationship (OR 1.16 per g/dL; 95% CI, 0.87–1.54; P = .32) (Fig 4B). The effect of VE was particularly evident at high baseline hemoglobin (>10 g/dL), where group A had a risk of short- and long-term complications of 88% (15/17), compared with only 29% (5/17) in group B (P = .01).

None of the patients in group B experienced any serious complications attributable to VE. In particular, there was no significant between-group difference in blood pressure despite the induced FO in group B (Table 2), and the 1 patient who showed clinical signs compatible with FO (hypertension) late in the course of the disease recovered quickly after a single dose of furosemide.

DISCUSSION

The results of our study show, for the first time, that VE early in the course of STEC-HUS has an important and positive impact on case fatality rate, CNS involvement, need for RRT, and long-term outcomes, thus significantly reducing the individual and health care disease burden.

In patients with STEC infection treated before HUS onset, the potential role of FI in mitigating subsequent TMA is not a new concept, and it is also well known that hemoconcentration (a surrogate marker of dehydration) in patients with active STEC-HUS is associated with more severe disease. However, it is not known whether VE early in the course of the disease can have beneficial effects after HUS has developed, given the already ongoing TMA and acute multiorgan injury.

Because there is no specific treatment for STEC-HUS, it is possible only to use support measures (transfusions, dialysis, antihypertensive medications, and appropriate nutrition), including the management of fluids, which traditionally relies on avoiding FO because patients often have oliguria if not outright anuria.
However, because the disease follows several days of diarrhea and reduced food intake, it is not unusual that patients are dehydrated and hemoconcentrated at TMA onset. As many as 33% of the patients herein described had normal to high hemoglobin levels at the time of diagnosis despite the ongoing hemolytic process, and this finding can be explained only by a concomitant hemoconcentration.

In the case of ongoing TMA, dehydration may not be easy to identify. Laboratory results are of little help because of capillary protein leakage caused by endothelial damage and severe proteinuria with consequent low plasma protein levels; therefore, it is unrealistic to confirm dehydration on the basis of normal plasma protein concentrations. The same is true for hematocrit (usually elevated in the case of dehydration) because of the hemolytic nature of the disease. Finally, weight loss is also unreliable because it is often partially or totally counterbalanced by peripheral edema (reduced onchotic pressure).

These diagnostic dilemmas and uncertainties at the bedside of a child with AKI and an impending risk of anuria mean that caregivers tend to be very careful in administering fluids.

In the case of intravascular volume depletion and associated hemoconcentration, TMA will be more severe as a result of 2 mechanisms: first, it increases blood viscosity, which, in addition to reducing organ perfusion per se, favors the formation of thrombi that ultimately will again reduce organ perfusion; second, the reduced blood flow not only leads to direct hypoperfusion but also favors the formation of thrombi by slowing blood circulation, thus reducing the blood supply to peripheral tissues. Both mechanisms ultimately decrease cell oxygenation and increase ischemic tissue damage.

Given this pathophysiology, it is clearly theoretically possible that early VE may be able to reduce or even prevent severe renal and other organ tissue damage by improving organ perfusion, minimizing ischemia, preventing glomerular tubular imbalance, and maintaining tubular flow. The lower LDH level in group B suggests that the beneficial effect of VE involves also systemic organ perfusion because the very high levels reached in HUS are not explained by hemolysis alone but are the result of multiorgan ischemic tissue damage.

In this study, early VE has obtained a >50% decrease in the need for RRT (26% vs 57%) compared with standard treatment. It seems important to point out that an extensive meta-analysis (total of 1370 cases) leads to an overall rate of dialysis in STEC-HUS of 60.1% (mean of all rates reported and weighted for numerosity).16

### TABLE 3 Comparison of Short- and Long-Term Outcomes in Patients Addressed to Early FI (Group B) and in Controls (Group A)

<table>
<thead>
<tr>
<th>Outcomes during acute phase</th>
<th>Controls (N = 38)</th>
<th>Volume Expansion (N = 38)</th>
<th>RR/GMR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, N (%)</td>
<td>2 (5.2)</td>
<td>0 (0)</td>
<td>NA</td>
<td>.49</td>
</tr>
<tr>
<td>CNS involvement, N (%)</td>
<td>22 (57.9)</td>
<td>10 (26.3)</td>
<td>0.45 (0.25–0.83)</td>
<td>.01</td>
</tr>
<tr>
<td>Need for RRT, N (%)</td>
<td>12 (7–18)</td>
<td>9 (7–12)</td>
<td>0.75 (0.59–0.96)</td>
<td>.02</td>
</tr>
<tr>
<td>Days in PICU, median (IQR)</td>
<td>8.5 (3.5–15.5)</td>
<td>2 (1–4.5)</td>
<td>0.31 (0.12–0.82)</td>
<td>.02</td>
</tr>
</tbody>
</table>

**Long-term outcomes**

| Extrarenal sequelae, N (%) | Controls (N = 38) | 1 (2.6) | 0 (0) | NA | .99 |
| Renal sequelae             |                   |         |       |    |    |
| Major (GKD II–V), N (%)    | 1 (2.6)           | 0 (0)   | NA    | .49 |
| Minor (GKD I), N (%)       | 12 (34.3)         | 5 (13.2) | 0.38 (0.15–0.89) | .03 |
| Total patients with long-term sequelae, N (%) | 15 (39.5) | 5 (13.2) | 0.33 (0.13–0.83) | .01 |

GMR, geometric mean ratio; NA, not applicable.

a 8 patients in group A and 8 patients in group B.

b Because renal and extrarenal sequelae are not mutually exclusive, the total of long-term sequelae exceeds the number of patients.

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**FIGURE 3**

Rate of need for RRT in historical controls and in patients actively infused and respective peak of sCr in dialyzed and nondialyzed patients.
Our observation that the actively infused patients showed a significant decrease in uric acid concentration, whereas >75% of the patients undergoing standard management had uric acid levels potentially in the range of nephrotoxicity (IQR 8.1–11.5 mg/dL at 48 hours), suggests that the better outcome may have resulted from reduced urate toxicity.

Obviously, the generous FI with AKI carries the risk of fluid retention and FO. Hyponatremia can be avoided by using isotonic solutions, and the risk of FO requires careful and frequent monitoring of the patient’s hydration status, including body weight every 12 hours, blood pressure, urine output, and occasionally, in unclear situations, the evaluation of intravascular volume by means of echocardiography or other noninvasive devices. In our experience FO has never been an issue for severe intravascular depletion because of the aforementioned conditions typically associated with STEC-HUS (dehydration and capillary leakage). Indeed, our “treat to weight” infusion regimen might underestimate intravascular needs given the considerable and ongoing vascular leakage, and the same needs might be different at various stages of illness.

The current study has 2 major limitations, because of its retrospective nature, but once it became obvious that the infused patients were doing a lot better, it seemed unethical to perform a randomized clinical trial that would have denied some patients a potentially life-saving treatment. The first limitation is that the patients undergoing early VE (group B) had lower sCr levels at baseline because they might have benefited from the early diagnosis, and consequent earlier referral to a specialized center, allowed by our screening program for STEC infection and the associated greater awareness of STEC-HUS among the pediatricians in our catchment area, as suggested (although not proven) by the median days of illness before HUS diagnosis in the 2 groups (6 vs 4). Although they may have been diagnosed earlier, their lower nadir platelet counts (Fig 2D) clearly exclude milder disease. Furthermore, the ORs provided were all adjusted for baseline sCr, as well as the other relevant baseline variables. In addition, we think that early diagnosis alone cannot explain the clearly milder course of the disease in group B. In this regard, we emphasize that the 2 fatal cases in group A were both diagnosed early (with sCr <2 mg/dL), but the early referral per se could not prevent the severe CNS involvement leading to death. It can be argued that the increased awareness in the catchment area has led to the diagnosis of milder cases (previously undiagnosed), and this might have caused an overrepresentation of milder cases in group B, thus explaining the better outcomes attributed to VE. To dispel any possible doubt, we made an additional analysis restricted to the more severe cases (baseline sCr >2 mg/dL) in both groups, which confirmed the better outcomes in group B. The second possible limitation is that changes in our RRT policy over time may have led to a treatment bias; this possibility was carefully considered, but the patients undergoing RRT in both groups had the same mean peak sCr and urea levels as those who did not, suggesting that such a change did not occur (Fig 3). Finally, it can be argued that the better laboratory values observed in group B could merely be the result of solute dilution, but the increase in body weight (12%) cannot account for the observed differences in solutes concentrations.

CONCLUSIONS

Our experience indicates that support measures aimed at inducing VE by means of active infusions early after a diagnosis of STEC-HUS can greatly improve TMA-related indicators and both the short- and long-term outcome, reducing the individual burden and social costs. Fluid status of patients with HUS should be carefully assessed at diagnosis (particularly if hematocrit >30%). Even at an early stage of the disease, when only bloody diarrhea is present, these children should be vigorously hydrated. Intravascular dehydration should be checked immediately upon admission and, if confirmed, promptly corrected by administering...
isotonic saline solution, regardless of plasma protein levels.

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ABBREVIATIONS

AKI: acute kidney injury
CI: confidence interval
CKD: chronic kidney disease
CNS: central nervous system
eGFR: estimated glomerular filtration rate
FI: fluid infusion
FO: fluid overload
HUS: hemolytic uremic syndrome
IQR: interquartile range
LDH: lactate dehydrogenase
OR: odds ratio
RR: relative risk
RRT: renal replacement therapy
sCr: serum creatinine
STEC-HUS: Shiga toxin–producing Escherichia coli hemolytic uremic syndrome
Stx: Shiga toxin
TMA: thrombotic microangiopathy
VE: volume expansion
WW: working weight

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