Relative Nephroprotection During Escherichia coli O157:H7 Infections: Association With Intravenous Volume Expansion

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ABSTRACT. Objective. The hemolytic uremic syndrome (HUS) consists of hemolytic anemia, thrombocytopenia, and renal failure. HUS is often precipitated by gastrointestinal infection with Shiga toxin–producing Escherichia coli and is characterized by a variety of prothrombotic host abnormalities. In much of the world, E coli O157:H7 is the major cause of HUS. HUS can be categorized as either oligoanuric (which probably signifies acute tubular necrosis) or nonoligoanuric. Children with oligoanuric renal failure during HUS generally require dialysis, have more complicated courses, and are probably at increased risk for chronic sequelae than are children who experience nonoligoanuric HUS. Oligoanuric HUS should be avoided, if possible. The presentation to medical care of a child with definite or possible E coli O157:H7 infections but before HUS ensues affords a potential opportunity to ameliorate the course of the subsequent renal failure. However, it is not known whether events that occur early in E coli O157:H7 infections, particularly measures to expand circulating volume, affect the likelihood of experiencing oligoanuric HUS if renal failure develops. We attempted to assess whether pre-HUS interventions and events, especially the volume and sodium content of intravenous fluids administered early in illness, affect the risk for developing oligoanuric HUS after E coli O157:H7 infections.

Methods. We performed a prospective cohort study of 29 children with HUS that was confirmed microbiologically to be caused by E coli O157:H7. Infected children were enrolled when they presented with acute bloody diarrhea or as contacts of patients who were known to be infected with E coli O157:H7, or if they had culture-confirmed infection, or if they presented with HUS. HUS was defined as hemolytic anemia (hematocrit <30%, with fragmented erythrocytes on peripheral-blood smear), thrombocytopenia (platelet count of <150,000/mm3), and renal insufficiency (serum creatinine concentration that exceeded the upper limit of normal for age). A wide range of pre-HUS variables, including demographic factors, clinical history, medications given, initial laboratory values, and volume and content of parenteral fluid administered, were recorded and entered into analysis. Estimates of odds ratios were adjusted for possible confounding effects using logistic regression analysis. Twenty-nine children who were <10 years old, had HUS confirmed to be caused by E coli O157:H7, and were hospitalized at the Children’s Hospital and Regional Medical Center, Seattle, were studied. The main outcome measured was development of oligoanuric renal failure. Oligoanuria was defined as a urine output <0.5 mL/kg per hour for at least 24 consecutive hours.

Results. As a group, the children with oligoanuric renal failure presented to medical attention and were evaluated with laboratory testing later than the children with nonoligoanuric renal failure. On initial assessments, the children with oligoanuric outcomes had higher white blood cell counts, lower platelet counts and hematocrits, and higher creatinine concentrations than the children with nonoligoanuric outcomes, but these determinations probably reflect later points of these initial determinations, often when HUS was already developing. Stool cultures were obtained (medians of 3 vs 2 days, respectively) and positive (medians of 7 vs 4 days, respectively) at later points in illness in the children in the oligoanuric than in the nonoligoanuric group. Intravenous volume expansion began later in illness in the children who subsequently developed oligoanuric renal failure than in those whose renal failure was nonoligoanuric (medians: 4.5 vs 3.0 days, respectively). Moreover, the 13 patients with nonoligoanuric renal failure received more intravenous fluid and sodium before HUS developed (1.7- and 2.5-fold differences, respectively, between medians) than the 16 patients with oligoanuric renal failure. These differences were even greater when the first 4 days of illness were examined, with 17.1- and 21.8-fold differences, respectively, between medians. In a multivariate analysis adjusted for age, gender, antibiotic use, and free water volume administered intravenously to these children during the first 4 days of illness, the amount of sodium infused remained associated with protection against developing oligoanuric HUS. Dialysis was used in each of the children with oligoanuric renal failure and in none of the children with nonoligoanuric renal failure. The median length of stay in hospital after the diagnosis of HUS was 12 days in the oligoanuric group and 6 days in the nonoligoanuric group.

Conclusions. Early recognition of and parenteral volume expansion during E coli O157:H7 infections, well before HUS develops, is associated with attenuated renal injury failure. Parenteral hydration in children who are possibly infected with E coli O157:H7, at the time of presentation with bloody diarrhea and in advance of
culture results, is a practice that can accelerate the start of volume expansion during the important pre-HUS interval. Rapid assessment of stools for \textit{E coli} O157:H7 by microbiologists and reporting of presumptive positives immediately can alert practitioners that patients are at risk for developing HUS and can prompt volume expansion in children who are not already being so treated. Our data also suggest that isotonic intravenous solutions might be superior to hypotonic fluids for use as maintenance fluids. Children who are infected with \textit{E coli} O157:H7 and are given intravenous volume expansion need careful monitoring. This monitoring should be even more assiduous as HUS evolves. \textit{Pediatrics} 2005; 115:e673–e680. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2236; acute tubular necrosis, \textit{Escherichia coli} O157:H7, hemolytic uremic syndrome, isotonic crystalloid, sodium.

**ABBREVIATIONS.** HUS, hemolytic uremic syndrome; OR, odds ratio; CI, confidence interval.

The hemolytic uremic syndrome (HUS) follows ~15% of culture-proven childhood \textit{Escherichia coli} O157:H7 infections and occurs ~1 week after diarrhea begins.\textsuperscript{1,5} Oligoanuric renal failure during HUS usually necessitates dialysis and lengthens hospitalization; its occurrence and duration are risk factors for chronic sequelae.\textsuperscript{6–15} Ideally, the oligoanuric form of HUS should be prevented, because oligoanuria seems to represent a more severe form of renal injury.

Vascular injury and prothrombotic coagulation abnormalities, such as thrombin generation, fibrinolysis inhibition, intravascular fibrin accretion,\textsuperscript{9} elevated circulating platelet activating factor,\textsuperscript{16} and degraded von Willebrand factor multimers,\textsuperscript{17} precede renal injury in infected children. These findings suggest that vascular occlusion, a process that conceivably could be attenuated by volume expansion, at least partly underlies renal insufficiency during HUS. We examined children with HUS in a prospective study of \textit{E coli} O157:H7 infections to determine whether any factors or events, particularly those relating to volume expansion that could affect renal perfusion, before HUS evolves are associated with a diminished occurrence of oligoanuria.

**METHODS**

**Patients and Clinical Data**

This study was approved by an Institutional Review Board (or equivalent group) for each participating institution. HUS was defined by the presence of hemolytic anemia (hematocrit of <30%, with fragmented erythrocytes on peripheral-blood smear), thrombocytopenia (platelet count of <150 000/mm\(^3\)), and renal insufficiency (serum creatinine concentration that exceeded the upper limit of normal for age).\textsuperscript{18} Oligoanuria was defined by the presence of hemolytic anemia (hematocrit of 30%, bocytopenia (platelet count of <150 000/mm\(^3\)), and renal insufficiency (serum creatinine concentration that exceeded the upper limit of normal for age).\textsuperscript{18} Oligoanuria was defined as a urine output <0.5 mL/kg per hour\textsuperscript{19} for ≥24 consecutive hours.

Children who were <10 years old and had HUS caused by \textit{E coli} O157:H7 entered the study by belonging to 1 of 4 groups: group 1, children in whom \textit{E coli} O157:H7 was recovered by stool culture from microbiologists in Washington, Oregon, and Idaho; group 2, children who had diarrhea and were contacts of children with culture-proven \textit{E coli} O157:H7 infection; group 3, children who were admitted to the Seattle Children’s Hospital and Regional Medical Center with acute bloody diarrhea; or group 4, children who had HUS preceded by diarrhea. After notification, we requested that the treating physician seek the patient’s family permission for us to approach them about participating in the study. When permission was granted, we explained to the family the purpose of the research and obtained written informed consent from the child’s parent or guardian and assent from the child when appropriate. Data were analyzed from children in groups 1, 2, 3, and 4 only when they developed HUS and were hospitalized at Children’s Hospital and Regional Medical Center during their HUS and from children who were enrolled in groups 2, 3, and 4 only when their stool yielded \textit{E coli} O157:H7. We encouraged the use of intravenous isotonic crystalloid\textsuperscript{20} until renal insufficiency necessitated restrictions in the patients who were enrolled and subsequently developed HUS. However, treating physicians were responsible for all fluids that were administered before and after enrollment.

A standardized questionnaire was administered to each child’s caregiver to determine when the diarrhea began and which medications were taken. The first day of diarrhea was considered to be the first day of illness. The days of illness on which stools were submitted for culture and on which \textit{E coli} O157:H7 was presumptively identified were analyzed as factors after microbiologic diagnosis. However, when \textit{E coli} O157:H7 was isolated after HUS was diagnosed, we used the day that HUS developed as the day of isolation. This alternative assignment was made because we believed that microbiologic diagnosis after HUS onset was unlikely to have influenced management. The period of risk for developing HUS was considered to be 14 days after the onset of diarrhea, in accordance with results from previous Washington State studies.\textsuperscript{2,4}

Laboratory and nursing records from all facilities where patients were evaluated and treated were reviewed to verify criteria fulfillment and record medications administered, volume and content of fluids infused on each day during the pre-HUS interval (defined as the period between the first day of diarrhea and the day before HUS was diagnosed, to avoid analyzing fluids that were restricted because of concerns about overload in patients with established or evolving renal failure), patient height and weight, initial white blood cell and platelet counts, serum creatinine and urea nitrogen concentrations, and serum sodium concentration when HUS developed. The volumes and sodium contents of all intravenously administered fluids were divided by body surface area.\textsuperscript{21} On day 9 or 10 of illness and only 1 or 2 days before the case definition of HUS was met, blood urea nitrogen was apparent, 3 patients received 100, 250, or 360 mL of packed erythrocytes, and 1 received 68 mL of 25% albumin, estimated as equivalent to receiving 30% and 100%, respectively, of the transfused volumes as 0.9% saline. Free water was calculated according to the following equation: free water = (mL of intravenous fluid) − [(mL of intravenous fluid) × (mEq/L sodium in the intravenous fluid/154 mEq/L)].

**Statistical Analysis**

Differences between the children who developed oligoanuria and those who did not were tested for significance using the 2-tailed Fisher exact test for proportions and the Mann-Whitney test for medians. First, we related outcome to fluids administered during the entire pre-HUS interval and then during the first 4 days of diarrhea. The first 4 days of illness, which are, in most cases, is the more standardized and interpretable of the intervals, because it represents the same fixed period for all patients. In contrast, fluids that were administered during the entire pre-HUS phase varied according to the day the therapy was initiated and the day on which HUS developed.

We used multivariate logistic regression analysis to examine the association between sodium infused early in illness and the development of oligoanuria, adjusting for age, gender, pre-HUS antibiotic use, and free water administration. These variables were chosen for their potential to influence the relationship between intravenous sodium administration and the subsequent development of oligoanuria. The associations between oligoanuria and the independent variables were estimated by odds ratios, which were calculated from the logistic regression coefficients and their standard errors and reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and 2-tailed P values.

Data were analyzed using SPSS (version 11.0 for Macintosh OX, SPSS, Inc, Chicago, IL). Figures were created in SPLUS (version 6, Insight, Inc, Seattle, WA).
RESULTS

Between May 1, 1997, and May 1, 2003, 29 children who were <10 years old and had HUS caused by E coli O157:H7 were treated at the Children’s Hospital and Regional Medical Center (Table 1). As a group, the 16 children with oligoanuric HUS, all of whom were dialyzed, had significantly higher initial white blood cell counts and serum creatinine concentrations, lower platelet counts, and longer hospital stays after the diagnosis of HUS than did the 13 patients with nonoligoanuric HUS, none of whom were dialyzed. The children in the oligoanuric group resembled those in the nonoligoanuric in terms of demographic characteristics, rates of vomiting and bloody diarrhea, and day of onset of HUS but had later median days of illness on which they (or their caregivers) noticed bloody diarrhea (3.0 vs 2.0; \( P = .047 \); among the 14 and 12 patients, respectively, whose stools were noted to contain gross blood), presented to medical attention (3.0 vs 2.0; \( P = .066 \)), submitted stool for culture (3.0 vs 2.0; \( P = .016 \)), underwent initial creatinine (4.5 vs 3.0; \( P = .023 \)) and white blood cell (5.0 vs 3.0; \( P = .079 \)) determinations, and were determined to be infected with E coli O157:H7 (or day of onset of HUS when the culture was reported as being positive after that point; 7.0 vs 4.0; \( P = .001 \); Fig 1 and Table 1).

Patients in the oligoanuric group received significantly less intravenous fluid volumes and sodium (1.7- and 2.5-fold differences in median values; \( P = .019 \) and 0.004, respectively) than those with nonoligoanuric renal failure during the entire pre-HUS period. When the analysis was confined to the first 4 days of illness, the differences in fluid and sodium administration were magnified (17.1- and 21.8-fold differences in median values; \( P = .002 \) and 0.001, respectively). Moreover, during the first 4 days of illness, children who subsequently developed oligoanuric HUS were significantly less likely than those in the nonoligoanuric group to have received any intravenous fluids (\( P = .02 \)). In neither interval did the free water volumes that were received by members of the 2 groups differ significantly (Table 1 and Fig 2). The serum sodium concentrations at HUS onset were significantly higher in the nonoligoanuric group than in the oliganuric group (137 vs 132 mEq/L; range: 132–140 vs 125–138 mEq/L, respectively; \( P = .001 \)).

We next performed a logistic regression analysis to examine the effects of a variety of factors on the likelihood of developing oligoanuric HUS. The total amount of sodium infused was significantly associated with a diminished oligoanuria rate (adjusted OR: 0.995; 95% CI: 0.990–0.999; \( P = .019 \)), but age (OR: 1.773; 95% CI: 0.810–3.882; \( P = .152 \)), gender (OR: 1.930; 95% CI: 0.167–22.259; \( P = .598 \)), frequency of administration of pre-HUS antibiotics (OR: 1.183; 95% CI: 0.084–16.576; \( P = .901 \)), and free water contained in intravenous fluids that were administered during the first 4 days of illness (OR: 1.000; 95% CI: 0.999–1.001; \( P = .519 \)) were not.

Table 2 shows the decrease in the likelihood of developing oligoanuria by increased amounts of intravenous sodium given in the first 4 days of illness, controlled for age, gender, antibiotic usage, and free water administered. For example, when comparing one child who received 100 mEq/m² sodium more than another, the risk for developing oligoanuric HUS in the former is 59% that of the latter, all other variables being equal.

DISCUSSION

Volume expansion during acute E coli O157:H7 infection might counteract the consequences of small vessel thrombi by improving renal perfusion, preventing glomerular tubular imbalance from hypoperfusion and ischemia, and maintaining tubular flow. Volume expansion might also mitigate the nephrotoxicities of filtered urate and hemoglobin and of Shiga toxin’s effects on renal tubular epithelial cells and monocytes that are independent of thrombotic changes. Indeed, salt loading protects against presumably nonthrombotic nephrotoxicity, such as that caused by amphotericin, and isotonic saline prevents nephropathy caused by radiocontrast media better than does hypotonic saline.

It is interesting that unlike a Minnesota study that suggested that antibiotic administration was related to a milder course of HUS, we detected no statistically significant association between antibiotic administration and development of either oligoanuria or nonoligoanuria. However, in our study, children who received antibiotics generally also received less intravenous sodium and fluids. Thus, it is plausible that the chief determinant of oligoanuria is inadequate volume expansion pre-HUS, not antibiotics.

We have encouraged hospitalizing children who are infected with E coli O157:H7 and then administering intravenous isotonic fluids for a variety of reasons: mandated contact precautions for hospitalized patients who are infected with E coli O157:H7 are too stringent to be provided by caregivers at home. Vomiting complicates attempts to provide oral rehydration, and oral hypotonic fluids will not expand intravascular volume as well as isotonic fluids that are administered intravenously. Also, we have observed that boluses of intravenous isotonic fluids frequently diminish the discomfort associated with eating or drinking during E coli O157:H7 infections.

Additional considerations prompt avoidance of hypotonic “maintenance” fluids, even if diarrheal losses are replaced with isotonic crystalloid. First, stool volumes are difficult to quantify in young children, because urine and feces are often mixed. Second, hypotonic fluids can lead to hyponatremia, which might lower the seizure threshold. Third, isotonic fluids have been proposed to be generally safer than hypotonic intravenous fluids in hospitalized children. Fourth, one can easily underestimate the degree of volume depletion during E coli O157:H7 infections because vascular injury causes extracellular fluid leakage. The resulting edema not only complicates intravascular volume status assessment but also obligates additional intravascular re-
<table>
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<tr>
<th>Characteristic</th>
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<th>With Oligoanuria</th>
<th>Without Oligoanuria</th>
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<td>Female gender, n (%)</td>
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<tr>
<td>Bloody diarrhea, n (%)</td>
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<td>14 (87.5)</td>
<td>12 (92.3)</td>
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<td>Vomiting, n (%)</td>
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<td>Antibiotics before HUS, n (%)</td>
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<td>Antimotility agents before HUS, n (%)</td>
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<td>Serum sodium concentration on first day of HUS, mEq/L</td>
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<td>8</td>
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<tr>
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<td>8</td>
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<td>Range</td>
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<tr>
<td>Intravenous fluids received before onset of HUS</td>
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<tr>
<td>Children receiving intravenous fluids at any time before diagnosis of HUS being made, n (%)</td>
<td>25 (89.7)</td>
<td>13 (81.3)</td>
<td>12 (92.3)</td>
<td>.606</td>
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<td>Volume of intravenous fluids administered at any time before diagnosis of HUS being made, L/m²</td>
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<td>2.44–20.53</td>
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<td>Sodium administered via intravenous fluids at any time before diagnosis of HUS being made, mEq/m²</td>
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<td>Free water administered as intravenous fluids at any time before diagnosis of HUS being made, L/m²</td>
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<tr>
<td>Children who received intravenous fluids in the first 4 d of illness, n (%)</td>
<td>20 (69.0)</td>
<td>8 (50.0)</td>
<td>12 (92.3)</td>
<td>.020</td>
</tr>
</tbody>
</table>

Day 1 of illness was defined as the first day of diarrhea. — indicates that the variable is not applicable.

* Blood was not observed in the stool in 2 children in the oligoanuric group and in 1 child in the nonoligoanuric group.

† Number of days that patients were hospitalized after the diagnosis of HUS.
pletion to maintain organ perfusion, which is better provided by isotonic fluids.

The inferred advantage of isotonic (compared with hypotonic) solutions for infusion at volumes that are appropriate for physiologic conditions is illustrated by a hypothetical infected 4-year-old. If that child weighs 16 kg and is 106 cm tall, then he or she will have a body surface area of 0.69 m². If that child is admitted at the beginning of day 4 of illness and receives a 20 mL/kg bolus of 0.9% saline on presentation and intravenous fluids for 24 hours at 1500 mL/m² of body surface area per day34 that contains 0.9%, 0.45%, or 0.23% saline, then that child will be given 208, 129, or 89 mEq/m² body surface area of intravenous sodium during the first 4 days of illness. Only the first of these values falls above the 25th percentile of sodium received by children in the nonoligoanuric group in this study.

One patient required pleural effusion drainage and another was intubated overnight because of pulmonary edema 2 and 4 days, respectively, after HUS onset, but we identified no other complications that seemed to be related to pre-HUS fluids in this series. These 2 patients each had nonoligoanuric renal failure and received less than the median fluid volume and sodium for that group pre-HUS. The causal association between pre-HUS fluids and the complications in these 2 children is uncertain because pulmonary problems during HUS are not rare; for example, in a 1993 E coli O157:H7 outbreak, in an era before volume expansion was used extensively in infected children, 9 of 37 HUS patients had respiratory complications.35

No patient experienced clinically significant vascular overload36 or hypernatremia, a potential complication of isotonic maintenance fluids,37 before HUS developed. In fact, our data suggest that pre-HUS volume expansion is associated with protection against hypernatremia, because patients with normal serum sodium concentrations at the onset of HUS tended to have nonoligoanuric HUS and also to have received intravenous volume expansion early in illness. Nonetheless, the use of any intravenous fluids in this setting warrants careful monitoring.

Children who develop azotemia yet are still urinating present particular challenges. Continued volume expansion might yield additional renal protection, but if acute tubular necrosis is inevitable, then such fluids might precipitate pulmonary overload. Therefore, we strongly encourage the hospitalization of such patients in institutions that are skilled in monitoring children for signs of and treating central volume overload and hypertension to reduce salt and water infusion rates if and when hypertension or cardiopulmonary overload occurs and to obtain pediatric nephrology consultation when renal insufficiency develops. However, if a child can be monitored assiduously, then we do not believe that fluids or sodium needs restricting merely because the serum creatinine concentration is rising.

Children who present early in illness during E coli O157:H7 infections have higher rates of developing
HUS, possibly because they have more fulminant and severe vascular injury. However, infected children who are presented for medical attention early in illness present a paradox: although they are more likely to develop HUS, they also stand to benefit from an opportunity to receive parenteral volume expansion well before renal insufficiency ensues, during a interval when such therapy is presumably safe. Therefore, we encourage hospitalization and isotonic volume expansion and fluid maintenance in advance of recovering E coli O157:H7 from patients with bloody diarrhea or symptomatic contacts of infected patients, because the critical interval during which this expansion might be beneficial is not known and might be short. We continue this therapy until the platelet count rises or the clinical condition obligates fluid and salt curtailment.

E coli O157:H7 detection provides another opportunity to alert clinicians that a patient is at risk for developing renal failure, because volume expansion and isotonic fluid maintenance can be started at that point in patients who are not already receiving this intervention. In fact, our analysis understates the association between timely and accurate microbiologic diagnosis and a good outcome, because in 3 oligoanuric patients, we counted the day of microbiologic diagnosis as being the day of onset of HUS, although E coli O157:H7 was isolated later in illness.

Several study limitations warrant comment. Most important, children who received intravenous volume expansion early in illness might have differed fundamentally from those who did not receive this support. However, none of our data, including an intensive interrogation of critical events early in illness, suggested bias or any differences between the 2 groups of children; the initial (and often abnormal) laboratory values in the oligoanuric group often reflected early HUS, because they were obtained considerably later in illness. In fact, the earlier median onset of bloody diarrhea and presentations to medical attention of children in the nonoligoanuric group suggest that these patients might have actually had more fulminant illnesses, because their symptoms prompted earlier and more extensive laboratory testing and volume expansion. Thus, the simplest explanation for the better outcomes in the children who were evaluated early is that they received early vol-

Fig 2. Volume and characteristics of fluids that were administered during first 4 days of illness. Vertical box-plot depiction of fluids that were administered to children with E coli O157:H7–associated HUS within the first 4 days of illness and characterization of the resulting renal failure. Shown for each factor is the distribution of values from the first 4 days of illness for the 13 children with nonoligoanuric renal failure and the 16 children with oligoanuric renal failure. The horizontal line with a diamond within each box represents the median; the lower and upper borders of each box represent the 25th and the 75th percentiles, respectively; and the T bars represent the differences between the lower and upper borders multiplied by 1.5. Values outside these boundaries are depicted as single points. A, Total intravenous fluids administered. B, Total intravenous sodium administered. C, Total free water administered, with 1 outlying value of 5.34 L/m² in the nonoligoanuric group (not shown).

TABLE 2. Increasing Sodium Administered During First 4 Days of Illness and Associated ORs of Developing Oligoanuric HUS

<table>
<thead>
<tr>
<th>Increase in Sodium, mEq/m²</th>
<th>OR of Developing Oligoanuria</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.949</td>
<td>0.908–0.991</td>
</tr>
<tr>
<td>20</td>
<td>0.900</td>
<td>0.825–0.982</td>
</tr>
<tr>
<td>50</td>
<td>0.769</td>
<td>0.618–0.958</td>
</tr>
<tr>
<td>100</td>
<td>0.592</td>
<td>0.381–0.918</td>
</tr>
</tbody>
</table>
ume expansion, not that they had milder illness. We also considered the remote possibility that the trans-
fusion of erythrocytes to 3 patients might have influ-
enced their course by neutralizing Shiga toxin ab-
sorbed from the gut, but we believe that this is un-
likely to have been the case because (1) erythro-
cytes do not bind Shiga toxin that is produced by E coli O157:H7 at body temperature38; (2) antigens that
are expressed on host erythrocytes, including P1, do
not have a clear relation to HUS risk39; (3) the distri-
bution of the multiple patients’ blood types, which
clearly comprise more red cell mass than the trans-
fused cells, was an imponderable; and (4) patients in
this series rarely have toxin in their stool as HUS
develops.40 Moreover, these 3 patients received a
transfusion on day 9 or 10 of illness, 1 or 2 days in
advance of meeting the case definition of HUS and
well after the vascular injury commenced.

A randomized, controlled trial of intravenous flu-
ids would be an ideal test of the value of volume
expansion during E coli O157:H7 infections. How-
ever, patients seek and receive medical attention at
multiple different venues and points in illness and
are often not recognized early in illness as being
infected with a pathogen that causes renal failure.
Moreover, withholding fluids from control patients
who have a dehydrating illness and are at risk for
developing subsequent renal failure would be uneth-
ical. An alternative method to confirm or refute our
findings is to perform this analysis in different pop-
ulations of children with well-characterized anteced-
ent infections.

Our data do not permit us to recommend the
optimal saline of intravenous fluids or the duration
of their administration; it is possible that the sus-
tained infusion beyond the first 4 days of illness
extended the benefit. Also, we could not examine the
influence of fluids taken by mouth, because it was
impossible to determine accurately their volumes or
sodium contents. In addition, our data do not ad-
dress whether intravenous volume expansion dimin-
ishes the risk for developing HUS among infected
children. However, data11,13 suggest that the differ-
etiation between oligoanuric HUS and nonoligo-
anuric HUS is at least as consequential as the differ-
etiation between uncomplicated gastrointestinal
infection and nonoligoanuric HUS. Finally, our an-
alysis does not consider the costs and risks of hospi-
talization for children who are not destined to
develop HUS, but we believe that there is considerable
potential benefit to volume expansion, in aggregate
and in individual cases, if this intervention can con-
vert a case of oligoanuric HUS to nonoligoanuric
HUS, as suggested by our data.

CONCLUSIONS
Ambulatory practitioners rarely have opportuni-
ties to recognize patients at such an appreciable and
predictable risk of shortly developing oligoanuric
renal failure as are children who are infected with E coli O157:H7. Oligoanuria or its duration during
HUS is associated with worse outcomes6–14 and
should be avoided.15 At our institutions, we encour-
age starting intravenous isotonic volume expansion
as early as possible in E coli O157:H7 infections, even
before culture results are known. Volume expa-
ansion’s benefits are harmonious with our emerging
understanding of HUS pathophysiology. However,
renal injury can still follow E coli O157:H7 infections
in well-hydrated children. The way to prevent HUS
is to prevent infections with E coli O157:H7.

ACKNOWLEDGMENTS
This research was supported by National Institutes of Health grant 1RO1DK52081.
We are indebted to Jennifer L. Bradley for assistance in prepar-
ing the manuscript; Jody Mooney and Jodi Smith for data re-
trieval; and the participating children, families, microbiologists,
other members of the laboratory staff, nurses, and physicians.

REFERENCES
1. Wong CS, Jelacic S, Habeeb RL, et al. The risk of the hemolytic-uremic syndrome after antibiotic treatment of Enterococci coli O157:H7 infec-
hemolytic uremic syndrome: importance of early cultures in establish-
cgi/content/full/100/1/12
5. Ostroff SM, Kobayashi JS, Lewis JH. Infections with Escherichia coli
O157:H7 in Washington State. The first year of statewide disease sur-
6. Gianantonio CA, Vitacca M, Mendilaharzu F, et al. The hemolytic-
uremic syndrome. Renal status of 76 patients at long-term follow-up.
7. Gianantonio CA, Vitacca M, Mendilaharzu F, et al. The hemolytic-
8. Dolislager D, Tune B. The hemolytic-uremic syndrome: spectrum of
9. de Jong M, Mornens L. Haemolytic-uremic syndrome: a 10-year fol-
10. Robson WL, Pick GH, Wilson PC. Prognostic factors in typical postdi-
1991;118:195–200
12. Robson WL, Leung AK, Brant R. Relationship of the recovery in the
glomerular filtration rate to the duration of anuria in diarrhea-
13. Tonshoff B, Sammet A, Sanden I, et al. Outcome and prognostic deter-
minants in the hemolytic uremic syndrome of children. Nephron. 1994;
68:63–70
diarrhea-associated hemolytic uremic syndrome: a systematic review,
meta-analysis, and meta-regression. JAMA. 2003;290:1360–1370
16. Smith JM, Jones F, Ciol MA, et al. Platelet-activating factor and Esche-
Willebrand factor-cleaving metalloproteinase activity in Escherichia coli
653–659
pediatric reference intervals for biochemical analytes as measured with
19. Flanichus L, Chelsan PS, Dasta JF. Quantitative effects of low-dose
dopamine on urine output in oligrmic surgical intensive care unit pa-
30:735–751, 2001

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