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Early Volume Expansion During Diarrhea and Relative Nephroprotection During Subsequent Hemolytic Uremic Syndrome

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Editor's Note: There have been more than 3000 cases of enterohemorrhagic *Escherichia coli* infections and more than 900 cases of hemolytic uremic syndrome reported in 16 countries in Europe and North America since the *E coli* outbreak began in Germany on May 1, 2011. This multicenter study provides strong evidence that intravenous volume expansion during the first 4 days of diarrhea due to *E coli* O157:H7 infection may protect from oligoanuria in children who subsequently develop hemolytic uremic syndrome. Because of the important public health implications of this study, we have decided to publish this article quickly online ahead of print.

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Abstract

Objectives—To determine if interventions during the pre–hemolytic uremic syndrome (HUS) diarrhea phase are associated with maintenance of urine output during HUS.

Design—Prospective observational cohort study.

Settings—Eleven pediatric hospitals in the United States and Scotland.

Participants—Children younger than 18 years with diarrhea-associated HUS (hematocrit level <30% with smear evidence of intravascular erythrocyte destruction), thrombocytopenia (platelet count $<150 \times 10^3/mm^3$), and impaired renal function (serum creatinine concentration>upper limit of reference range for age).

Interventions—Intravenous fluid was given within the first 4 days of the onset of diarrhea.

Outcome Measure—Presence or absence of oligoanuria (urine output ≤0.5 mL/kg/h for >1 day).

Results—The overall oligoanuric rate of the 50 participants was 68%, but was 84% among those who received no intravenous fluids in the first 4 days of illness. The relative risk of oligoanuria when fluids were not given in this interval was 1.6 (95% confidence interval, 1.1–2.4; P=.02). Children with oligoanuric HUS were given less total intravenous fluid (r = −0.32; P = .02) and sodium (r=−0.27; P=.05) in the first 4 days of illness than those without oligoanuria. In multivariable analysis, the most significant covariate was volume infused, but volume and sodium strongly covaried.

Conclusions—Intravenous volume expansion is an underused intervention that could decrease the frequency of oligoanuric renal failure in patients at risk of HUS.

Hemolytic uremic syndrome (HUS) consists of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure and typically follows diarrhea caused by Shiga toxin-producing bacteria, especially *Escherichia coli* O157:H7. Patients with oligoanuric HUS usually need dialysis and have longer hospitalizations[1] and higher frequencies of chronic sequelae[2–16] than those with nonoligoanuric HUS. No therapy has been demonstrated to prevent HUS or to reduce the severity of kidney injury once HUS is established.[17] However, the pathophysiologic cascade leading to renal failure might provide an opportunity to mitigate renal damage. Specifically, current models for HUS pathogenesis posit that Shiga toxins produced by intestinal *E coli* gain access to the circulation, injure renal microvasculature, and generate thrombi that likely contribute to renal ischemia; this process precedes HUS.[17–19] If patients at risk for HUS are recognized early in illness, then the brief interval between first presentation with diarrhea and HUS onset could be exploited to maintain or improve renal perfusion, possibly averting renal shutdown. Indeed, children infected with *E coli* O157:H7, the predominant cause of HUS worldwide, usually present with an easily-profiled set of symptoms and findings: diarrhea that is initially nonbloody but that becomes bloody 1 to 3 days later, 5 or more bowel movements in the 24 hours prior to initial evaluation, abdominal tenderness, abdominal pain that increases around the act of

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defecation, and lack of fever at time of presentation (despite often reporting a history of fever prior to evaluation).[17,18,20–24]

Adequate kidney perfusion is advisable in all patients at risk of acute renal failure.[25] In one single-center study of children younger than 10 years, intravenous volume expansion during the first 4 days of *E coli* O157: H7–related diarrhea was strongly associated with protection from oligoanuria during subsequent HUS.[1] Here, we tested whether or not the findings of this predecessor study could be replicated and generalized across multiple centers and in older children. To do so, we conducted a prospective observational cohort study of children younger than 18 years who were hospitalized with diarrhea-associated HUS in 11 pediatric referral centers in the United States and Scotland. We analyzed all independent variables preceding the development of HUS to determine if any might have influenced the nonoligoanuric vs oligoanuric outcomes.

METHODS

Patients younger than 18 years, an age interval that represents approximately 90% of cases of diarrhea-associated HUS in North America,[26] were included if they had a postdiarrheal illness that met the case definition of HUS[1,18,19,22,27]: anemia (hematocrit level <30% with smear evidence of intravascular erythrocyte destruction; to convert to proportion of 1.0, multiply by 0.01), thrombocytopenia (platelet count $<150\times10^3/mm^3$), and renal insufficiency (serum creatinine concentration>upper limit of reference range for age). Exclusion criteria consisted of inability to obtain consent or identify the first day of diarrhea and concerns about stress of study participation on families. Potential participants were prospectively identified by site investigators at each institution as soon as possible after a diagnosis of HUS was made, while these patients were still hospitalized. Each site principal investigator approached subjects' families and requested permission to notify an investigator at Washington University (C.A.H.). After written informed consent was obtained from a parent or guardian, a single investigator (C.A.H.) administered a face-to-face (St Louis Children's Hospital) or telephone (all other sites) standardized questionnaire. This instrument was designed to reconstruct the sequence of events and presence and timing of all signs, symptoms, interventions, and venues of interventions between diarrhea onset and HUS diagnosis. All clinical decisions before and during HUS were made at the discretion of each patient's care provider(s); care was independent of study participation. Printed records were collected to verify inclusion criteria, medications given, test results, patient height and weight, and timing, content, and volume of intravenous fluids infused. Institutional review board approval was obtained at each participating site.

Daily intravenous fluids were calculated from midnight to midnight (1 calendar day), local time. We totaled all fluid volume (liters) and sodium (milliequivalents) given intravenously during each of the pre-HUS days, and then divided these values by body surface area (m^2) to normalize these interventions to patient size.

Oligoanuric or nonoligoanuric status was assigned after discharge, when all hospital information was provided. All data were double-entered by a single investigator (C.A.H.) into a Microsoft Excel spreadsheet (Microsoft, Redmond, Washington) to reduce entry

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errors. Six charts were randomly selected for re-extraction to confirm the accuracy of our data-gathering methodology.

The first days of illness and of HUS were defined, respectively, as the first day of diarrhea and the first day on which each laboratory abnormality defining HUS was present. The outcome of interest was presence of oligoanuria, defined as urine output of less than 0.5 mL/kg/h for at least 1 calendar day after HUS onset.[1] Oligoanuria duration was defined as the number of consecutive calendar days from the first day of oligoanuria until the day before the resuming urine output first exceeded the oligoanuric threshold, inclusive.

The statistical significance of differences between categorical variables for the oligoanuric and the nonoligoanuric groups was determined by χ^2 or 2-tailed Fisher exact test when expected values for each cell were less than 5. The significance of differences between medians for continuous values was determined by the Mann-Whitney *U* test (2 tailed), as data were not normally distributed. We also determined a *U* statistic (denoted by *U*) and the *r* value, showing effect size (medium effect is defined as $r > |0.3|$ and large effect is defined as $r > |0.5|$). We estimated that 14 children in each group (oligoanuric and nonoligoanuric) were needed to demonstrate a difference in outcome at an α level of .05 with 80% power, based on the predecessor study.[1] However, because we did not assign urine output status until all data had been extracted and reviewed and the occurrence of oligoanuria exceeded projections, we enrolled more than our target goal.

We used our χ^2 model to determine the relative risk of oligoanuria when fluids were not given vs when they were given in the first 4 days of illness. To adjust for potential confounding variables, we performed a logistic regression. An initial model was created from variables that could plausibly alter the risk of oligoanuria: age, antibiotics given, and intravenous volume and sodium administered in the first 4 days. Covariates were tested for multicolinearity (variance <0.8 and the variance inflation factor <3). The covariate chosen to remain in the model was the one with the greatest significance in the original model. The second model included only covariates that were nominally significant at $P<.20$ and had no colinear covariates. The final model included only significant covariates that were statistically significant at $P<.05$. Data were analyzed using SPSS (version 17.0 for Windows; SPSS Inc, Chicago, Illinois).

RESULTS

Between July 1, 2007, and December 1, 2008, 61 patients were eligible for inclusion; 11 were not enrolled because of language barriers and a lack of interpreter available for consent (n=6), concerns regarding family stress (n=2), denial of consent (n=2), and inability to identify the first day of diarrhea (n=1). The 50 participants were enrolled in St Louis (n=12), Glasgow (n=11), Seattle (n=7), Sacramento (n=4), Memphis, Little Rock, Milwaukee, Cincinnati (n=3 each), Columbus (n=2), Albuquerque, and Indianapolis (n = 1 each). The 34 patients (68%) with oligoanuric HUS were distributed among the St Louis (n=8), Glasgow (n=10), Seattle (n=5), Sacramento (n=3), Memphis, Little Rock, Cincinnati (n=2 each), Milwaukee, and Indianapolis (n=1 each) sites. Typically, a brief period of oliguria preceded prolonged anuria in the oligoanuric HUS group.

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The oligoanuric and nonoligoanuric groups were similar in terms of their demographic characteristics and symptoms and the medications that they received before the diagnosis of HUS (Table 1). The 2 groups also had considerable overlap in initial laboratory values, though the oligoanuric group was evaluated later and their laboratory test values reflected expected deteriorations as early HUS was developing (Table 2). However, children who developed oligoanuric HUS received less volume and less sodium during the entire pre-HUS interval than those whose HUS was nonoligoanuric (Table 3). The difference was even more pronounced when earlier fluid administration was analyzed; in the first 4 days of illness, 84% of the children (21 of 25) who received no intravenous fluids developed oligoanuria but only 52% of the children (13 of 25) receiving any intravenous fluid in that interval developed oligoanuric HUS. Children were 1.6 times more likely (95% confidence interval, 1.1–2.4; P=.02) to become oligoanuric if no intravenous fluids were given during the first 4 pre-HUS days. Children whose HUS was classified as oligoanuric received medians of 0 L of intravenous fluid and 0 mEq of intravenous sodium in the first 4 days of illness, while the corresponding medians in children whose HUS was nonoligoanuric were 1.7 L/m^2 (U=170; r=−0.32; P=.02) and 189 mEq/m^2 (U=185; r=−0.27; P=.05), respectively.

The initial logistic regression model included the covariates of age, antibiotics used, and intravenous volume and sodium during the first 4 days of illness. Age was omitted from the second model because of a P value of .25. Antibiotics were omitted from the model because of a P value of .09. When these covariates were tested for multicolinearity, the total volume and sodium received by the children during the first 4 days were colinear with variance inflation factors of 8.6 and 8.5, respectively. Volume was retained in the final model because it was the variable with greatest significance in the first model. The final logistic regression model contained only 1 variable: total volume infused during the first 4 days of illness, which was statistically significant (Table 4).

Of the 34 children with oligoanuric HUS, 33 reached the oligoanuric threshold before day 10 of illness. Six patients had serious extrarenal complications of HUS; 1 nonoligoanuric and 2 oligoanuric patients had clinically significant pancreatitis, 1 nonoligoanuric patient had a seizure, and 2 oligoanuric patients had respiratory distress necessitating intubation. One of the 2 intubated patients had a left lower lobe infiltrate and pleural effusion; her initial tracheal aspirate yielded pneumococci (she was also infected with *E coli* O157:H7). The other intubated patient had pancreatitis, a thrombotic stroke, insulin-dependent diabetes, left ventricular dysfunction, and left pleural effusion and was intubated 6 days after HUS was diagnosed. Preintubation chest x-ray interpretation commented principally on the enlarging pleural effusion but also mentioned possible fluid overload. There was no association between these nonrenal complications and the amount of fluid volume and sodium given during illness. However, no patient was admitted with, or required ventilatory assistance because of, acute pulmonary edema, and no patient died.

COMMENT

This study associates intravenous volume expansion during the first 4 days of illness in children who subsequently develop HUS with a nonoligoanuric outcome. Two findings support this conclusion. First, most children who received no intravenous fluids in this

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period developed oligoanuric HUS, whereas only half of those who received any fluids in this interval developed this less desirable outcome (the quantities of sodium and fluids correspondingly also differed between groups). Second, multivariable analysis confirmed that fluid volume given in the first 4 days of illness was significantly associated with nephro-protection after controlling for other variables that might have affected the development of oligoanuria.

It is notable that the median total volume of fluids (0.05 L/m^2) and sodium (7.8 mEq/m^2) given to patients in the first 4 days of illness in the current study were 1 to 2 orders of magnitude lower than in the predecessor study (2.5 L/m^2 and 201 mEq/m^2, respectively),[1] but a beneficial effect of this intervention was still identified. Indeed, the different degrees of association with nephro-protection in the 2 studies confer a dose-response validation to the observed benefits of the association. This study also serves to generalize the findings of the predecessor study by extending the results to an older group of children and to multiple centers.

It is concerning that 14 of the 39 subjects who were evaluated during the first 4 days of illness received no intravenous fluids, and of those who did, few received the volume or sodium content we have recommended, namely, intravenous isotonic crystalloid given as a bolus and then as a maintenance infusion to bolster renal perfusion.[1,20] Opportunities to provide volume expansion in that critical interval appear, therefore, to have been lost. Study authors treated only 3 of the patients in the first 4 days of illness, so the largely nonprotocolized and widely varying care we describe probably reflects current practice in the United States and Scotland.

Delayed microbiological diagnosis might have contributed to delayed intervention because treating physicians might not have recognized that these patients were at risk of developing HUS without the prompting provided by a positive stool culture. Indeed, in the predecessor study, early culture result notification to the requesting physician was associated with earlier hydration and better outcome.[1] However, in this study, nearly half of the patients with HUS tested negative for Shiga toxin–producing *E coli*, as is common when stools from children with HUS are sent for microbiologic examination late in illness.[26,27] Point of presentation care could be improved by rapid, reliable diagnostics that identify patients infected with pathogens with appreciable chances of causing HUS. At St Louis Children’s Hospital, we optimize current technology by plating specimens on receipt (ie, not waiting until the morning) and notifying requesting physicians of presumptively positive *E coli* O157:H7 (appropriately agglutinating sorbitol nonfermenting colonies) tests in advance of confirming that the organism is *E coli* and determining the H antigen. These policies have reduced the interval between specimen receipt in the laboratory and preliminary reporting to approximately 24 hours (P. Sellenriek, BS, MBA, and C.-A. Burnham, PhD, unpublished data, July 2011).

We considered the possibility that providers hesitated to give fluids to children who were on the verge of developing HUS. However, half or fewer of the children in this cohort underwent any testing, received any intravenous fluids, or were admitted to any hospital in

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the first 4 days of illness, well before HUS is diagnosed. Such inaction does not reflect major provider concerns about impending renal failure at the initial encounter.

This study has several limitations. Our data do not allow us to address the optimal sodium content of the fluid given, but because sodium and fluid volume (ie, water independent of sodium content) covaried, we continue to recommend isotonic and not hypotonic crystalloid for volume expansion. We also cannot determine the value or safety of isotonic intravenous volume expansion in children whose serum creatinine concentrations are rising but who are still urinating. However, our data suggest that if oligoanuria does not occur by day 10 of illness, this undesirable outcome has probably been averted. Identifying such a point in illness after which additional fluids might not benefit patients is helpful to clinicians who should strive to avoid cardiopulmonary overload. Relevant to this point, it is notable that no study patient, including those whose fluids were not restricted as HUS developed, was intubated because of acute pulmonary edema.

A randomized controlled trial might avoid potentially confounding factors that could have separated the oligoanuric and nonoligoanuric groups for reasons other than volume expansion. However, a trial to test the efficacy of isotonic intravenous volume expansion would face many challenges. As demonstrated in this article, there are difficulties recognizing this rare infection early in illness, and such patients present to many different sites for initial care but usually not to the medical center at which HUS is ultimately treated. Also, a trial of the efficacy of isotonic intravenous volume expansion would require careful consideration of control treatment, as potential participants will always have diarrhea and are almost always vomiting. Such patients are quite likely experiencing diminished renal blood flow and are at risk of oligoanuric renal failure in the week after presentation.

In summary, intravenous volume expansion early in illness was associated with better renal outcome during HUS in this second, and independent, systematic cohort study of pre-HUS clinical events and variables. Clinical profiling can identify patients who might be infected with *E coli* O157:H7 (detailed in several reviews[17,20]) and are at risk of developing HUS. Expeditious microbiological diagnosis and hospitalization of possibly infected patients is encouraged[28] because the interval during which volume expansion is most effective and safest might be brief. An added benefit to hospitalization is that this intervention diminishes secondary infections in the community.[29]

Because presence and/or duration of oligoanuria are so repeatedly associated with long-term sequelae in children with HUS, it seems appropriate to prioritize maintenance of urine output during HUS, even though our data do not permit us to state that pre-HUS intravenous volume expansion prevents long-term renal sequelae. Intravenous volume expansion appears to be a logical strategy that can be used now to achieve this goal, because we cannot hasten renal recovery once oligoanuria is established. We reiterate that volume expansion in these situations must be accompanied by assiduous monitoring for cardiopulmonary overload and hypertension.[17,20] However, volume expansion does not completely protect against oligoanuria during HUS. The surest way to prevent oligoanuric HUS is to prevent *E coli* O157:H7 infections.

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Table 1

Categorical Variables in the Oligoanuric and Nonoligoanuric Groups

Characteristic	Patients, No. (%)			OR (95% CI)	*P* Value
	All (n = 50)	Oligoanuric (n = 34)	Nonoligoanuric (n = 16)		
Female sex	32 (64)	22 (64.7)	10 (62.5)	0.9 (0.3–3.1)	.88
Race					
White	47 (94)	33 (97.1)	14 (87.5)	0.2 (0.2–2.5)	.24
White/black	2 (4)	1 (2.9)	1 (6.3)	2.2 (0.–37.6)	.54
White/Asian	1 (2)	0 (0)	1 (6.3)	NA	.32
Stool culture positive for *E coli* O157:H7	27 (54)	18 (52.9)	9 (56.3)	1.1 (0.3–3.8)	.83
E coli O121:H19	1 (2)	0 (0)	1 (6.3)	NA	.32
Bloody diarrhea[a]	42 (85.7)	28 (84.8)	14 (87.5)	1.3 (0.3–7.3)	>.99
Vomiting	48 (96)	32 (94.1)	16 (100)	NA	>.99
Antimotility agents before HUS	21 (42)	14 (14.2)	7 (43.8)	1.1 (0.3–3.7)	.86
Antibiotics before HUS	18 (36)	10 (29.4)	8 (50)	2.4 (0.7–8.2)	.16
Fever[b]	22 (44)	16 (47)	6 (37.5)	0.7 (0.2–2.3)	.53

Abbreviations: CI, confidence interval; HUS, hemolytic uremic syndrome; NA, not applicable; OR, odds ratio.

[a] One oligoanuric case was excluded from this analysis because of uncertainty regarding blood in stool, so the denominator is 49 for all patients and 33 for oligoanuric patients for this variable.

[b] Fever as reported by family.

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Table 2

Demographic, Laboratory, and Clinical Continuous Variables in the Oligoanuric and Nonoligoanuric Groups

Variable	Median (Range) [IQR]			*U*	Effect Size (*r*)[a]	*P* Value
	All Patients (n = 50)	Anuric Patients (n = 34)	Nonoligoanuric Patients (n = 16)			
Age, y	4.1 (1.0 to 17.2) [5.5]	3.9 (1.0 to 13.4) [4.6]	5.3 (1.2 to 17.2) [8.3]	228	−0.13	.36
Duration of illness at first symptom, d						
Bloody stool[b]	3 (1 to 5) [2]	3 (1 to 5) [2]	3 (1 to 4) [1.5]	186.5	−0.04	.8
Evaluated	3 (1 to 8) [2]	3 (1 to 8) [3]	2.5 (1 to 5) [1]	183.5	−0.27	.06
Intravenous fluid	4 (1 to 15) [3]	5 (1 to 11) [3]	3.5 (1 to 15) [3.3]	207.5	−0.19	.18
Blood test	4 (1 to 15) [2]	4 (1 to 11) [2]	3 (1 to 15) [1.8]	191	−0.24	.09
Stool culture	4 (1 to 21) [2.3]	4 (1 to 10) [3]	3.5 (1 to 21) [2.5]	213.5	−0.17	.22
Initial laboratory values						
WBC, No./mm^3	14.5 (5.2 to 44.7) [11.1]	15.4 (5.2 to 44.7) [12.5]	12.1 (8.1 to 22.1) [5.5]	167.5	−0.27	.06
Hematocrit, %[c]	37.3 (12 to 49) [8.5]	37.8 (13 to 47) [9.2]	37.3 (12 to 49) [6.7]	236.5	−0.06	.69
Platelets, No. × 1000/mm^3[c,d]	257 (43 to 469) [211]	249 (43 to 469) [216]	275 (50 to 414) [191]	204	−0.11	.44
Sodium, mEq/L[c]	134 (121 to 144) [5]	133 (121 to 144) [5]	135 (130 to 141) [6]	151	−0.32	.02
Bicarbonate, mEq/L[c]	20 (7 to 29) [7]	20.5 (7 to 29) [8.3]	19 (11.7 to 27) [6]	246	−0.028	.85
Urea nitrogen, mg/dL[c]	16.5 (4 to 280) [37.1]	17.3 (4 to 273) [41]	15.5 (7 to 280) [21]	224.5	−0.095	.51
Creatinine, mg/dL[c]	0.5 (0.2 to 22.3) [1.7]	0.6 (0.3 to 22.3) [2.4]	0.4 (0.2 to 17.5) [0.5]	206	−0.15	.29
Sodium level on day HUS diagnosed, mEq/L[c]	134 (121 to 147) [6]	133 (121 to 143) [6.3]	135 (129 to 147) [6.5]	180	−0.27	.06
Duration, d						
Dialysis	5 (0 to >50) [13]	11.5 (0 to >50) [11]	0 (0 to 4) [0]	33	−0.71	<.001
Anuria[e]	1 (0 to 45) [4]	3 (1 to 45) [5.5]	0	16	−0.78	<.001
Hospital stay	14 (4 to 82) [11]	18 (7 to 82) [9]	9 (4 to 16) [5]	67	−0.6	<.001

Abbreviations: HUS, hemolytic uremic syndrome; IQR, interquartile range; WBC, white blood cells.

SI conversion factors: To convert bicarbonate to millimoles per liter, multiply by 1.0; creatinine to micromoles per liter, multiply by 88.4; hematocrit to proportion of 1.0, multiply by 0.01; and sodium to millimoles per liter, multiply by 1.0.

[a] Medium effect is defined as $r > |0.3|$.

[b] Of the 42 subjects with this history.

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[c] Laboratory data were not available for 1 nonoligoanuric patient until transfer to one of the study sites several days after onset of HUS.

[d] Platelet count not available for 1 additional nonoligoanuric patient early in illness, but other laboratory values are included.

[e] Precise day of onset of anuria not determined for 1 patient.

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Table 3

Differences in Total Fluid Volume and Sodium Given Intravenously to the Oligoanuric and Nonoligoanuric Groups

	Median (Range) [IQR]					
	All Patients (n = 50)	**Anuric Patients (n = 34)**	**Nonoligoanuric Patients (n = 16)**	***U***	**Effect Size (*r*)[a]**	***P* Value**
Total fluid volume, L/m^2						
During all days before HUS	1.5 (0.0–10.0) [4.3]	1.3 (0.0–9.5) [3.9]	3.8 (0.0–10.7) [6.7]	182	−0.26	.06
During first 4 days of illness	0.05 (0–7.5) [2.8]	0 (0–4.9) [1.7]	1.7 (0–7.5) [3.4]	170	−0.32	.02
Total sodium, mEq/m^2						
During all days before HUS	193 (0–1457) [483]	170 (0–1457) [430]	370 (0–1225) [551]	193	−0.23	.13
During first 4 days of illness	7.8 (0–755) [295]	0 (0–755) [220]	189 (0–483) [362]	185	−0.27	.05

Abbreviations: HUS, hemolytic uremic syndrome; IQR, interquartile range.

[a]Medium effect is defined as $r > |0.3|$.

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Table 4

Logistic Models

Logistic Model	Variable	Odds Ratio (95% Confidence Interval)
First	Age	1.1 (0.9–1.3)
	Antibiotics	2.9 (0.7–11.4)
	Total intravenous fluid given during the first 4 days of illness	6.1 (0.8–46.8)
	Total intravenous sodium given during the first 4 days of illness	1.0 (0.97–1.0)
Second[a]	Antibiotics	3.1 (0.8–11.9)
	Total intravenous fluid given during the first 4 days of illness	1.4 (1.0–2.0)
Final[b]	Total intravenous sodium given during the first 4 days of illness	1.4 (1.0–1.9)

[a] Variables with *P* values of greater than .20 were eliminated from the first model. Also, the colinear variable of sodium given in the first 4 days of illness was taken out because it had less significance than volume given.

[b] Variables with *P* values of greater than .05 were eliminated from the model. The final model has only volume given during the first 4 days.