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THE RISK OF THE HEMOLYTIC–UREMIC SYNDROME AFTER ANTIBIOTIC TREATMENT OF *ESCHERICHIA COLI* O157:H7 INFECTIONS

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Abstract

Background—Children with gastrointestinal infections caused by *Escherichia coli* O157:H7 are at risk for the hemolytic–uremic syndrome. Whether antibiotics alter this risk is unknown.

Methods—We conducted a prospective cohort study of 71 children younger than 10 years of age who had diarrhea caused by *E. coli* O157:H7 to assess whether antibiotic treatment in these children affects the risk of the hemolytic–uremic syndrome and to assess the influence of confounding factors on this outcome. Estimates of relative risks were adjusted for possible confounding effects with the use of logistic-regression analysis.

Results—Among the 71 children, 9 (13 percent) received antibiotics and the hemolytic–uremic syndrome developed in 10 (14 percent). Five of these 10 children had received antibiotics. Factors significantly associated with the hemolytic–uremic syndrome were a higher initial white-cell count (relative risk, 1.3; 95 percent confidence interval, 1.1 to 1.5), evaluation with stool culture soon after the onset of illness (relative risk, 0.3; 95 percent confidence interval, 0.2 to 0.8), and treatment with antibiotics (relative risk, 14.3; 95 percent confidence interval, 2.9 to 70.7). The clinical and laboratory characteristics of the 9 children who received antibiotics and the 62 who did not receive antibiotics were similar. In a multivariate analysis that was adjusted for the initial white-cell count and the day of illness on which stool was obtained for culture, antibiotic administration remained a risk factor for the development of the hemolytic–uremic syndrome (relative risk, 17.3; 95 percent confidence interval, 2.2 to 137).

Conclusions—Antibiotic treatment of children with *E. coli* O157:H7 infection increases the risk of the hemolytic–uremic syndrome.

Escherichia coli O157:H7 causes sporadic and epidemic gastrointestinal infections worldwide. In approximately 15 percent of the children in North America who are infected with *E. coli* O157:H7, the hemolytic–uremic syndrome develops soon after the onset of diarrhea.[1–4] This syndrome is characterized by thrombocytopenia, hemolytic anemia, and nephropathy and is believed to be caused by Shiga toxins elaborated by *E. coli* O157:H7 or other infecting *E. coli* that have been absorbed into the systemic circulation.[5]

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Treatment with antibiotics does not ameliorate *E. coli* O157:H7 infections,[1,6,7] and in some studies, it has been associated with worse clinical outcomes.[8–10] In one prospective, randomized, controlled trial, antibiotic treatment was neither harmful nor beneficial, but treatment was administered late in the course of illness.[11] In a child infected with *E. coli* O157:H7 who was treated with antibiotics before the onset of diarrhea, fecal shedding of the organisms ceased, but the treatment did not prevent the hemolytic–uremic syndrome.[12]

When analyzing the role of antibiotic administration as a risk factor for the development of the hemolytic–uremic syndrome in children infected with *E. coli* O157:H7, it is important to consider that the severity of illness might confound the association with antibiotic treatment. For example, antibiotics might be administered to more severely ill infected children in whom the hemolytic–uremic syndrome is destined to develop independently of antibiotic treatment. We therefore examined data from a prospective cohort study to determine whether antibiotic treatment alters the risk of the hemolytic–uremic syndrome among children infected with *E. coli* O157:H7.

METHODS

A network of 47 cooperating laboratories in Washington, Oregon, Idaho, and Wyoming prospectively identified 73 children younger than 10 years of age who had *E. coli* O157:H7 infections between April 1, 1997, and August 31, 1999. These children were identified on the basis of stool cultures done on sorbitol–Mac-Conkey agar to detect this pathogen.[13] One of the investigators was contacted immediately by telephone after the identification of each infected child by the laboratory. This investigator then immediately telephoned the child's physician seeking permission to approach the child's family about participation in the study. Written informed consent was obtained from the parents or guardians of each child, and, if appropriate, assent was obtained from the child. The study was approved by the institutional review board at each participating hospital. Only the 71 children whose stool cultures were obtained within the first seven days after the onset of illness (the first day of diarrhea was considered to be the first day of illness) were included in the analysis.

A standardized questionnaire was administered to the caregivers of each enrolled child within two days after enrollment. Questions were included about the child's sex, age, and race or ethnic group; the duration of symptoms and signs; the presence or absence of visible blood in the stool, vomiting, and fever; and the names of prescription and nonprescription medications taken during the illness. Prescription medications were administered at the discretion of each child's primary care, inpatient, or emergency department physician. Nonprescription medications were administered on the recommendation of each patient's treating physician or on the basis of the caregiver's decision. Only medications taken on or before the seventh day of illness were considered. Medications administered after the hemolytic–uremic syndrome was diagnosed were not analyzed. Medications were classified as antibiotics; antimotility drugs (if they inhibited intestinal peristalsis), including opioid narcotics; acetaminophen; and nonsteroidal antiinflammatory drugs.

The administration of all reported prescription drugs was verified by the medical provider who prescribed them or by inspecting the child's medical record. Isolates of *E. coli* O157:H7 were sent to the Children's Hospital and Regional Medical Center in Seattle for determinations of their susceptibility to the antibiotics administered to the children. The disk-diffusion technique was used for susceptibility testing.[14]

To reduce concern about observer error and the ability to validate temperature measurements, the analysis included only the initial temperature determinations for children evaluated at Children's Hospital and Regional Medical Center in Seattle. The laboratory

data that were analyzed consisted of white-cell counts and serum urea nitrogen and creatinine concentrations. Only the initial laboratory test result for each child was analyzed as a potential risk factor for the development of the hemolytic–uremic syndrome.

Daily blood counts and renal-function tests were performed in all infected children until the hemolytic–uremic syndrome developed and resolved or until the diarrhea resolved and the hemolytic–uremic syndrome clearly did not develop. The hemolytic–uremic syndrome was defined as hemolytic anemia (a hematocrit below 30 percent, with evidence of the destruction of erythrocytes on a peripheral-blood smear), thrombocytopenia (a platelet count of less than 150,000 per cubic millimeter), and renal insufficiency (a serum creatinine concentration that exceeded the upper limit of the normal range for age).

On the basis of previous studies in Washington of children infected with *E. coli* O157:H7,[1,2] the period of risk for the hemolytic–uremic syndrome was considered to be 14 days from the onset of diarrhea among children with a positive culture for *E. coli* O157:H7, and this represented the period of clinical observation. The incidence of the hemolytic–uremic syndrome was expressed in terms of the risk of development of the syndrome for an individual child during these 14 days. Children with the syndrome were categorized as having oligoanuria if they excreted less than 0.5 ml of urine per kilogram of body weight per hour for 48 or more hours during the course of the syndrome. Medical records were reviewed to verify the fulfillment of the classification criteria.

Differences between the children who were treated with antibiotics and those who were not were analyzed with the use of independent-sample t-tests for continuous variables and Fisher's exact or chi-square tests for categorical variables and with use of univariate logistic regression for linear trend.[15] Multivariate logistic-regression analysis was used to examine the risk of the hemolytic–uremic syndrome after adjustment for the initial white-cell count and the day of illness on which the initial stool culture was obtained for analysis.[15] These factors were chosen because they were associated with the risk of the hemolytic–uremic syndrome.[1,8] The day of submission of the stool sample was the most common point in the illness at which antibiotics were prescribed for the children in this study.

The association between the exposure to medication during the diarrheal phase of infection and the subsequent development of the hemolytic–uremic syndrome was estimated by odds ratios and reported as the relative risk. Demographic factors, the presence or absence of specific symptoms, the duration of the diarrhea before the laboratory assessments and the administration of antibiotics, and initial laboratory values were studied to determine whether these factors confounded the association between exposure to medication and the development of the hemolytic–uremic syndrome. We selected the variables that were significantly associated with the hemolytic–uremic syndrome, and were a priori considered to be potential confounders, to yield the most parsimonious model. After adjustment, the final models were interpreted as the adjusted relative risk of the hemolytic–uremic syndrome among children infected with *E. coli* O157:H7. Adjusted relative risks and their 95 percent confidence intervals were calculated from the logistic-regression coefficients and their standard errors. Results are reported as adjusted relative risks with 95 percent confidence intervals. All P values are two-tailed. Computations were performed with use of Intercooled Stata software (version 6.0 for Windows, Stata, College Station, Tex.).

RESULTS

The hemolytic–uremic syndrome developed in 10 of the 71 children with *E. coli* O157:H7 infection (14 percent). Four of these 10 children were classified as having oligoanuria, and each of these 4 required dialysis. Seven children required erythrocyte transfusions, platelet

transfusions, or both. None of the children died during hospitalization. The incidence of the hemolytic–uremic syndrome according to the children's characteristics is summarized in Table 1.

There were no significant differences in the frequency of the hemolytic–uremic syndrome with respect to sex and the presence or absence of bloody diarrhea, caregivers' reports of fever, and vomiting. Nor was the frequency significantly related to the initial serum urea nitrogen or creatinine concentration or, for the subgroup of children evaluated at Children's Hospital and Regional Medical Center, the initial temperature. However, the frequency of the syndrome was significantly related to the initial white-cell count (P=0.005), with a rate of 0 percent among children with an initial count of 3200 to 8700 per cubic millimeter, a rate of 6 percent among those with an initial count of 8800 to 11,800 per cubic millimeter, a rate of 17 percent among those with an initial count of 11,900 to 14,200 per cubic millimeter, and a rate of 35 percent among those with an initial count of 14,300 to 24,600 per cubic millimeter. In addition, the frequency of the syndrome was higher among children who had laboratory studies soon after the onset of illness (according to the day of illness on which the stool was obtained for culture, the day on which the culture was positive, and the day on which the initial white-cell count was obtained) and among those who were treated with antibiotics.

The hemolytic–uremic syndrome developed in 5 of the 9 children given antibiotics (56 percent), as compared with 5 of the 62 children who were not given antibiotics (8 percent, P<0.001). The characteristics of the children who were given antibiotics and those who were not were similar (Table 2).

We used logistic-regression analysis to assess demographic variables, symptoms, laboratory values, and medication use as potential risk factors for the hemolytic–uremic syndrome (Table 3). The initial white-cell count and the day of the initial stool culture — two surrogates for the severity of illness — were independently associated with the development of the syndrome. In the logistic-regression analysis of both factors, the initial white-cell count remained significantly associated with the hemolytic–uremic syndrome (P=0.02), with risk being proportional to the white-cell count. Also, the interval from the onset of diarrhea to the day on which the initial stool culture was obtained remained strongly associated with the risk of the hemolytic–uremic syndrome (P=0.008), with the risk being inversely proportional to the number of days in this interval.

Multivariate analysis, adjusted for the day on which the initial stool culture was obtained and the initial white-cell count, showed that children treated with antibiotics had a higher risk of the hemolytic–uremic syndrome than did children who did not receive antibiotics (adjusted relative risk, 17.3; 95 percent confidence interval, 2.2 to 137; P=0.007). Among the children who received antibiotics within the first three days after the onset of illness, the risk of the syndrome was increased in the univariate analysis (relative risk, 15.0; 95 percent confidence interval, 1.3 to 174; P=0.03) and after adjustment for the day on which the initial stool culture was obtained and the initial white-cell count in the multivariate analysis (adjusted relative risk, 32.3; 95 percent confidence interval, 1.4 to 737; P=0.03). Adjustment for other base-line covariates did not affect the significance of the association between antibiotic treatment and the development of the hemolytic–uremic syndrome (data not shown).

Of the 10 children in whom the hemolytic–uremic syndrome developed, 2 were treated with trimethoprim–sulfamethoxazole and 3 were treated with cephalosporins. Among the four antibiotic-treated children in whom the syndrome did not develop, one received trimethoprim–sulfamethoxazole, one a cephalosporin, and two amoxicillin. The relative risk

of the hemolytic–uremic syndrome as a function of the class of antibiotic used, after adjustment for the initial white-cell count, was 17.7 for trimethoprim–sulfamethoxazole (95 percent confidence interval, 1.2 to 261; P=0.04) and 13.4 for β-lactam antibiotics (95 percent confidence interval, 1.9 to 96; P=0.01). In each case, all *E. coli* O157:H7 strains isolated from the nine children who received antibiotics were susceptible to the drug taken by the child from whom the organisms were recovered.

DISCUSSION

This prospective cohort study demonstrates that among children infected with *E. coli* O157:H7, the hemolytic–uremic syndrome developed more often in those who were given antibiotics than in those who were not. We were unable to identify any characteristics that differentiated children who received antibiotics from those who did not.

Our data confirm that administering sulfa-containing antibiotics to children infected with *E. coli* O157:H7 increases their risk of the hemolytic–uremic syndrome[8,9] and indicate that β-lactam antibiotics are associated with a similar degree of risk. An extensive analysis of the *E. coli* O157:H7 outbreak in Sakai City, Japan, suggested that treatment with fos-fomycin was associated with a significantly decreased risk of the hemolytic–uremic syndrome,[16] but only for children who received the drug on the second day, but not on other days, of their illness. Also, fos-fomycin was compared only with other antibiotics, not with the absence of treatment with antibiotics, because as in other reports describing this outbreak,[16–25] almost all children received antibiotics.

We noticed an inverse relation between the risk of the hemolytic–uremic syndrome and the length of the interval between the onset of diarrhea and the day on which the initial stool culture was obtained. This inverse relation could represent the presence of a more fulminant course that prompted earlier evaluation and therefore reflected more severe extraintestinal injury in infected children who were at greater risk for the syndrome whether or not antibiotics were prescribed. However, multivariate analysis did not diminish the risk associated with antibiotic administration when this factor was considered.

We did not find an association between the reported presence of fever and the risk of the hemolytic–uremic syndrome, as has been found in some studies.[8,16] However, prehospitalization temperatures were determined by a variety of caregivers, using different instruments and techniques. Moreover, of the 18 children who were evaluated at Children's Hospital and Regional Medical Center, only 1 had a temperature exceeding 38.0°C on initial evaluation, and the hemolytic–uremic syndrome did not develop in this child. Also, despite the absence of an association between treatment with antimotility drugs or opioid narcotics and the risk of the hemolytic–uremic syndrome, we recommend against the use of these drugs in children with acute diarrhea, because of their reported association with complications of *E. coli* O157:H7 infection and with the prolongation of symptoms.[1,24,26–28]

Our data may have been confounded by selection bias, because we studied only children whose stools yielded *E. coli* O157:H7 as identified by our surveillance network. However, we are unable to assess the effect of antibiotic treatment in children infected with this pathogen whose illness was not diagnosed by our system of participating laboratories.

There are considerable data to support an association between the hemolytic–uremic syndrome and enteric infection with Shiga-toxin–producing bacteria.[2,5] Cytotoxin, presumably Shiga toxin, has been found in the stools of patients with both *E. coli* O157:H7 infection and the hemolytic–uremic syndrome.[5,29] In in vitro experiments, exposure to various antibiotics causes *E. coli* to release Shiga toxin.[30–33] Antibiotics might increase the

risk of the hemolytic–uremic syndrome by causing the release of Shiga toxin from injured bacteria in the intestine, making the toxin more available for absorption.

An observational study cannot completely eliminate other potential biases with respect to the association of antibiotics and the risk of the hemolytic–uremic syndrome, but our analysis has several strengths in comparison with previous attempts to assess the risks or benefits of antibiotic treatment of *E. coli* O157:H7 infections. Children's caregivers were questioned prospectively during the acute illness, reducing problems with recall that may occur when interviews are performed weeks or months after infection. Such a bias might pertain especially to the use of non-prescription drugs. Also, our study addressed the use of antibiotics in children infected with a variety of strains of *E. coli* O157:H7 and was not limited to children infected with the same strain, as is the case in analyses of outbreaks.[1,6,8,10,16–22] Thus, our data are broadly applicable to clinical practice, where physicians encounter children infected with one of many subtypes of this pathogen. Indeed, the variability among *E. coli* O157:H7 strains in the antibiotic-induced release of Shiga toxin[30] also suggests that conclusions from analyses of outbreaks may not be easily generalizable.

The association between antibiotic treatment and the development of the hemoltyic–uremic syndrome in children with *E. coli* O157:H7 infections is strong and plausible. We therefore recommend against giving antibiotics to children who may be infected with *E. coli* O157:H7 until the results of a stool culture indicate that the pathogen responsible is one that is appropriately treated by an antibiotic. Even if the small advantage associated with empirical fluoroquinolone therapy in some adults with acute diarrhea[34–36] holds true for children, we believe that the risk of administering antibiotics to children who might be infected with pathogens for which antibiotics are contraindicated (i.e., *E. coli* O157:H7) exceeds the potential benefit. However, it is important to remember that the hemolytic–uremic syndrome can occur even in infected children who have not been treated with antibiotics. Therefore, we believe that the hemolytic–uremic syndrome is best prevented by avoiding primary infection.

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Table 1

Frequency of the Hemolytic–Uremic Syndrome According to the Characteristics of 71 Children Infected with *Escherichia coli* O157:H7.*

Characteristic	Frequency of the Hemolytic– Uremic Syndrome %	No. of Cases/Total No. of Patients	P Value
Sex			0.96
Male	14	5/36	
Female	14	5/35	
Age			0.95†
0–1 yr	5	1/22	
2–3 yr	29	4/14	
4–6 yr	14	3/22	
7–10 yr	15	2/13	
Race or ethnic group			
White	15	9/62	0.63
Hispanic	0	0/3	—
Black	0	0/1	—
Asian or Pacific Islander	33	1/3	0.37
Native American	0	0/2	—
Bloody diarrhea			0.26
Yes	12	8/64	
No	29	2/7	
Vomiting			0.25
Yes	18	8/45	
No	8	2/26	
Fever‡			0.22
Yes	25	2/8	
No	6	1/16	
Initial white-cell count			0.005†
3200–8700/mm^3	0	0/18	
8800–11,800/mm^3	6	1/18	
11,900–14,200/mm^3	17	3/18	
14,300–24,600/mm^3	35	6/17	
No. of medications taken for *E. coli* infection			0.002†
0	4	2/46	
1	25	5/20	
2	60	3/5	
Acetaminophen			0.09
Yes	33	3/9	
No	11	7/62	
Nonsteroidal antiinflammatory drugs			—

Characteristic	Frequency of the Hemolytic–Uremic Syndrome %	No. of Cases/Total No. of Patients	P Value
Yes	0	0/1	
No	14	10/70	
Antimotility drugs			0.19
Yes	27	3/11	
No	12	7/60	
Antibiotics			0.001
Yes	56	5/9	
No	8	5/62	
Stool culture obtained[§]			0.01[†]
Days 1–2 of illness	33	8/24	
Day 3 of illness	9	2/22	
Days 4–7 of illness	0	0/25	
Antibiotics started[§¶]			0.69[†]
Day 1 of illness	50	2/4	
Day 2 of illness	67	2/3	
Day 3 of illness	50	1/2	
Initial white-cell count obtained[§]			0.009[†]
Days 1–3 of illness	28	7/25	
Days 4–5 of illness	12	3/25	
Days 6–10 of illness	0	0/21	
Stool culture positive for *E. coli* O157:H7[§]			0.04[†]
Days 2–4 of illness	25	6/24	
Day 5 of illness	16	3/19	
Days 6–10 of illness	4	1/28	

[*] Of the 18 children for whom the initial temperature was documented at Children's Hospital and Regional Medical Center (2 of whom had the hemolytic–uremic syndrome), all had temperatures of less than 38.0°C except for 1, who had a temperature of 39.4°C and in whom the hemolytic–uremic syndrome did not develop. All children had serum urea nitrogen concentrations of less than 20 mg per deciliter (7.1 mmol per liter), except for two whose serum urea nitrogen concentrations were 22 mg per deciliter (7.9 mmol per liter) and 47 mg per deciliter (16.8 mmol per liter), neither of whom had the hemolytic–uremic syndrome. All children had initial serum creatinine concentrations of less than 0.9 mg per deciliter (79.6 μmol per liter) except for one, who had a serum creatinine concentration of 1.0 mg per deciliter (88.4 μmol per liter) and in whom the hemolytic–uremic syndrome did not develop.

[†] The P value is for the linear trend for the variable.

[‡] The category of fever was based on the caregivers' reports and was added to the standardized questionnaire on December 1, 1998; thus, only 24 children were evaluated for this variable.

[§] The onset of diarrhea was considered to be the first day of illness.

[¶] This variable was assessed in the nine children who received antibiotics.

Table 2

Characteristics of Children Infected with *Escherichia coli* O157:H7 According to Whether They Were Treated with Antibiotics.*

Characteristic	Antibiotics (N=9)	No Antibiotics (N=62)	P Value
Female sex — no. (%)	6 (67)	29 (47)	0.30
Age — yr	5.5±3.4	4.1±2.6	0.15
Race or ethnic group — no. (%)			
White	8 (89)	54 (87)	1.00
Hispanic	0	3 (5)	1.00
Black	0	1 (2)	1.00
Asian or Pacific Islander	1 (11)	2 (3)	0.34
Native American	0	2 (3)	1.00
Bloody diarrhea — no. (%)	7 (78)	57 (92)	0.21
Vomiting — no. (%)	5 (56)	40 (65)	0.72
Fever — no. (%)†			
Yes	0	8 (38)	0.53
No	3 (100)	13 (62)	
Initial temperature — °C‡	37.0±1.0	36.9±0.8	0.88
Initial white-cell count — $\times 10^{-3}/mm^3$	13.1±4.7	11.6±4.2	0.34
Initial serum urea nitrogen — mg/dl§	9.2±2.7	10.2±6.1	0.63
Initial serum creatinine —mg/dl¶	0.4±0.1	0.4±0.1	0.71
Stool culture obtained — day of illness‖	2.7±1.4	3.3±1.4	0.19
Antibiotics started — day of illness‖	2.8±1.6	—	—
Initial white-cell count obtained — day of illness‖	4.0±2.0	4.7±2.0	0.30
Stool culture positive for *E. coli* O157:H7 — day of illness‖	4.9±1.3	5.3±1.6	0.42
Hemolytic–uremic syndrome case definition fulfilled — day of illness‖**	7.8±1.5	7.2±1.1	0.49
Progression to hemolytic–uremic syndrome — no. (%)			
Hemolytic–uremic syndrome	5 (56)	5 (8)	0.002
Oligoanuric hemolytic–uremic syndrome	2 (22)	2 (3)	

*Plus–minus values are means ±SD.

†The category of fever was based on the caregivers' reports and was added to the standardized questionnaire on December 1, 1998; thus, only 24 children were evaluated for this variable.

‡The initial temperature was documented in 18 children who presented to Children's Hospital and Regional Medical Center in Seattle (3 of whom received antibiotics).

§To convert values for serum urea nitrogen to millimoles per liter, multiply by 0.357.

¶To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

‖The onset of diarrhea was considered to be the first day of illness.

**This variable was assessed in the 10 children in whom the hemolytic–uremic syndrome developed.

Table 3

Relative Risk of the Hemolytic–Uremic Syndrome among Children Infected with *Escherichia coli* O157:H7.

Covariate*	Univariate Relative Risk (95% CI)†	P Value	Adjusted Relative Risk (95% CI)‡	P Value
Age (continuous)	1.0 (0.8 to 1.3)	0.95	1.1 (0.8 to 1.5)	0.43
0 to 5 yr§	1.0		1.0	
>5 yr	0.7 (0.2 to 2.8)	0.57	1.1 (0.2 to 5.7)	0.93
Sex				
Male§	1.0		1.0	
Female	1.0 (0.3 to 4.0)	0.96	1.1 (0.2 to 5.0)	0.95
Presence of bloody diarrhea	0.4 (0.1 to 2.2)	0.26	0.4 (0.1 to 3.0)	0.36
Presence of vomiting	2.6 (0.5 to 13.3)	0.25	3.2 (0.5 to 20.6)	0.21
Presence of fever¶	5.0 (0.4 to 66.0)	0.22	6.2 (0.2 to 169)	0.23
Temperature (continuous)‖	1.9 (0.5 to 7.4)	0.37	14.1 (0.5 to 419)	0.13
Initial serum urea nitrogen (continuous)**	1.0 (0.9 to 1.1)	0.73	1.1 (0.9 to 1.3)	0.53
2–10 mg/dl§	1.0		1.0	
≥11 mg/dl	2.2 (0.6 to 8.6)	0.25	2.8 (0.5 to 14.4)	0.23
Initial serum creatinine (continuous)††	0.7 (0.01 to 91.5)	0.89	4.7 (0.01 to >500)	0.62
0.1–0.5 mg/dl§	1.0		1.0	
≥0.6 mg/dl	1.2 (0.1 to 11.9)	0.85	3.0 (0.1 to 69.4)	0.50
Initial white-cell count (continuous)	1.3 (1.1 to 1.5)	0.005	1.5 (1.1 to 2.1)	0.02
3200–12,900/mm^3§	1.0		1.0	
≥13,000/mm^3	3.9 (1.0 to 15.5)	0.06	6.0 (1.2 to 29.8)	0.03
Day initial white-cell count obtained	0.5 (0.3 to 0.8)	0.009	0.7 (0.4 to 1.5)	0.38
Day stool culture obtained	0.3 (0.2 to 0.8)	0.01	0.3 (0.1 to 0.7)	0.008
Day stool culture positive	0.5 (0.3 to 1.0)	0.04	1.0 (0.5 to 2.1)	1.00
Acetaminophen given	3.9 (0.8 to 19.3)	0.09	2.0 (0.3 to 12.9)	0.46
Antimotility drugs given	2.8 (0.6 to 13.3)	0.19	3.0 (0.5 to 19.4)	0.25
Antibiotics given				
Within first 7 days after onset of illness	14.3 (2.9 to 70.7)	0.001	17.3 (2.2 to 137)	0.007
Within first 3 days after onset of illness	15.0 (1.3 to 174)	0.03	32.3 (1.4 to 737)	0.03

*Continuous covariates were analyzed and reported on continuous scales and are also presented as dichotomous groupings around the median. CI denotes confidence interval.

†Odds ratios were used to estimate relative risk.

‡The relative risk was adjusted for the initial white-cell count and the interval from the onset of diarrhea to the day on which the stool culture was obtained.

§This category served as the reference group.

¶The category of fever was based on the caregivers' reports and was added to the standardized questionnaire on December 1, 1998; thus, data on only 24 children were included in the analysis.

[//] The initial temperature was documented in 18 children who presented to Children's Hospital and Regional Medical Center in Seattle (2 of whom had the hemolytic–uremic syndrome).

[**] To convert values for serum urea nitrogen to millimoles per liter, multiply by 0.357.

[††] To convert values for serum creatinine to micromoles per liter, multiply by 88.4.