Hemolytic Uremic Syndrome After an *Escherichia coli* O111 Outbreak

Emily W. Piercefield, MD, DVM, MS, MPH; Kristy K. Bradley, DVM, MPH; Rebecca L. Coffman, RN, MPH; Sue M. Mallonee, RN, MPH

Background: In August 2008, the largest known US serotype 1 *Escherichia coli* O111 outbreak occurred in Oklahoma, causing 341 illnesses, including hemolytic uremic syndrome (HUS). HUS is not well described in non-O157 *E coli* outbreaks but occurs in 2% to 15% of O157 infections, predominantly among children. We examined outbreak-related hospitalizations to characterize *E coli* O111 illness, the HUS attack rate, and factors associated with subsequent HUS diagnosis among hospitalized patients.

Methods: Medical records were reviewed for clinical presentation and evidence of HUS among hospitalized patients identified during the outbreak investigation. Characteristics of hospitalized patients with vs without HUS were compared.

Results: HUS was identified in 26 of 156 (16.7%) confirmed or probable *E coli* O111 infections; 65.4% of patients with HUS required dialysis, and 1 patient died. The median age of patients with HUS was 43.5 years (age range, 1-88 years); adults composed 57.7% of HUS cases. Characteristics at hospital admission associated with subsequent HUS diagnosis included white blood cell count of at least 20 000/μL (adjusted odds ratio [aOR], 11.3; 95% confidence interval [CI], 1.7-75.3), elevated serum creatinine level for age (9.7; 1.4-69.2), and vomiting before hospital admission (6.8; 1.5-31.3). Administration of antimicrobial agents (risk ratio [RR], 1.0; 95% CI, 0.5-1.8) or medication with antimotility effects (1.4; 0.6-2.9) was not associated with subsequent HUS.

Conclusions: The HUS attack rate in this *E coli* O111 outbreak was comparable to that for *E coli* O157–related illnesses, but most cases occurred among adults. On admission, factors associated with subsequent HUS can identify patients who require close monitoring and early aggressive supportive care to improve outcomes.

Arch Intern Med. 2010;170(18):1656-1663

HEMOLYTIC UREMIC SYNdrome (HUS) is an illness characterized by acute kidney injury, thrombocytopenia, and microangiopathic hemolytic anemia. Many patients with HUS require dialysis during the acute illness, and some develop complications from HUS (eg, hypertension, neurologic deficits, or chronic kidney disease). Approximately 280 cases were reported in the United States in 2006, reflecting an incidence of 0.11 cases per 100 000 population; more than 50% occurred among children younger than 5 years.[1] HUS most commonly occurs after a diarrheal illness caused by infection with Shiga toxin–producing *Escherichia coli* (STEC). In the United States, the most common serotype in STEC gastrointestinal tract infections is O157, causing an estimated 73 000 illnesses annually,[2] with HUS developing in 2% to 15%.[3-6] Non-O157 STEC causes an estimated 37 000 illnesses annually in the United States.[2] After *E coli* O26, the second most common non-O157 STEC isolated from specimens submitted to the Centers for Disease Control and Prevention between 1983 and 2002 was the serotype *E coli* O111.[7] Similar to *E coli* O157, other serotypes can cause HUS, but the illness and HUS attack rates associated with non-O157 serotypes are not well characterized.

In an Australian laboratory between 1987 and 1994, *E coli* O111 accounted for 50% of non-O157 STEC isolated from patients with HUS.[8] In a 1995 Australian *E coli* O111 outbreak, 90% of 20 patients with HUS required dialysis, 65% experienced acute hypertension, 45% experienced central nervous system events, and 5% died.[9] Compared with sporadic HUS cases in Australia, the O111 outbreak had

CME available online at www.jamaarchivescme.com and questions on page 1620

Author Affiliations: Epidemic Intelligence Service Program, Centers for Disease Control and Prevention, assigned to the Oklahoma State Department of Health (Dr Piercefield), and the Oklahoma State Department of Health, Oklahoma City (Dr Bradley and Mss Coffman and Mallonnee). Dr Piercefield is now with the Scientific Education and Professional Development Program Office, Centers for Disease Control and Prevention, Atlanta, Georgia.

Table 1. Case Definitions for the 2008 *Escherichia coli* O111 Outbreak in Oklahoma

Case Category	Description
	***Escherichia coli* O111 Infection**
Confirmed	Consumed food from or had close contact with someone who consumed food from the implicated restaurant August 10-24, 2008, and had a diarrheal illness with ≥3 loose stools per day after the exposure date and either had (*a*) *E coli* O111 isolated with a pulsed field gel electrophoresis pattern matching the outbreak strain or (*b*) evidence of STEC by immunoassay and polymerase chain reaction for Shiga toxin–encoding genes
Probable	Consumed food from the implicated restaurant August 10-24, 2008, and either had hemolytic uremic syndrome or (*a*) a bloody diarrheal illness with ≥3 loose stools per day after the exposure date or (*b*) nonbloody diarrhea with ≥3 loose stools per day after the exposure date and (*c*) abdominal cramps along with evidence of STEC by immunoassay
Suspected	Consumed food from the implicated restaurant August 10-24, 2008, and had nonbloody diarrhea with ≥3 loose stools per day after the exposure date and abdominal cramps and no laboratory evidence of STEC infection
	Hemolytic Uremic Syndrome Case
Confirmed	Acute kidney injury,[a] and anemia,[b] and low blood platelets,[c] and microangiopathic changes[d]
Probable	Same description for confirmed case except that microangiopathic changes were not present or blood smear was not performed

Abbreviation: STEC, Shiga toxin–producing *E coli*.

SI conversion factors: To convert creatinine level to micromoles per liter, multiply by 88.4; hemoglobin level to grams per liter, multiply by 10.0; platelet count to $\times 10^9$/L, multiply by 1.0.

[a] Elevated serum creatinine level (≥1.0 mg/dL for age <13 y or ≥1.5 mg/dL for age ≥13 y) or both proteinuria and hematuria.

[b] Hemoglobin level less than 12 g/dL for female subjects or less than 13 g/dL for male subjects.

[c] Platelet count less than 150 $\times 10^3$/μL.

[d] Microangiopathic changes on peripheral blood smear (ie, schistocytes, burr cells, or helmet cells).

a larger proportion of cases with bloody stools, a higher rate of dialysis, and more chronic sequelae. Other STEC O111 outbreaks have been reported in Western Europe and Japan,[10-12] but only a limited number of STEC O111 outbreaks have been described in the United States.[13-16]

An outbreak of bloody diarrhea among patrons of an independently owned, country buffet–style restaurant in Oklahoma was caused by *E coli* O111:nonmotile. Restaurant exposure for all outbreak-related cases occurred August 10 2008, to August 24, 2008, and restaurant exposure dates for persons with confirmed O111 infections ranged from August 15, 2008, to August 24, 2008. Approximately 341 persons became ill (including 156 confirmed or probable STEC O111 cases and 185 suspected cases); 1 patient died and more than 70 were hospitalized, some with HUS. This is the largest reported outbreak of STEC O111 in the United States to date and the largest number of US outbreak–related HUS cases from a non-O157 STEC serotype. This study characterizes hospitalized patients associated with the *E coli* O111 outbreak to better understand the spectrum of non-O157 STEC illness and risk factors for HUS.

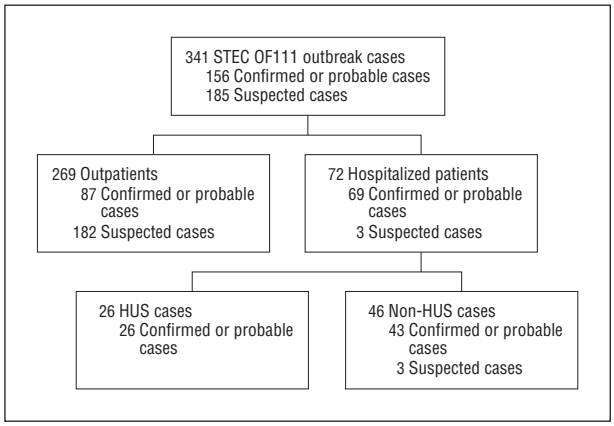

Figure. Classification of cases related to the 2008 *Escherichia coli* O111 outbreak in Oklahoma. HUS indicates hemolytic uremic syndrome; STEC, Shiga toxin–producing *E coli*.

METHODS

DEFINITIONS

Case definitions for outbreak-related *E coli* O111 illness and HUS classification for this study are given in **Table 1**. *Escherichia coli* O111 classifications for the overall outbreak and by hospitalization and HUS status are shown in the **Figure**. Patients with HUS had to have acute kidney injury, thrombocytopenia, and anemia with or without evidence of microangiopathic changes on blood smear. All hospitalized patients related to the overall outbreak who did not meet the case definition for confirmed or probable HUS were considered a comparison group of patients without HUS. Race/ethnicity was determined by self-report.

CASE SELECTION

Analysis was limited to 72 persons who met the following criteria for outbreak-related illness and were hospitalized for this illness: persons who had consumed food from the implicated restaurant August 10, 2008, through August 24, 2008, and were seen with gastrointestinal tract illness or HUS or persons who had culture-confirmed infection with the outbreak strain of *E*

Table 2. Demographics and Symptoms of Hospitalized Patients in the 2008 *Escherichia coli* O111 Outbreak in Oklahoma

Variable	No. (%)			Risk Ratio (95% Confidence Interval)
	All Hospitalized (n=72)	HUS Cases (n=26)	Non-HUS Cases (n=46)	
Age group, y				
0-4	**6** (8.3)	4 (15.4)	2 (4.4)	1.94 (0.94-4.03)
5-9	**6** (8.3)	2 (7.7)	4 (8.7)	0.97 (0.29-3.30)
10-17	**8** (11.1)	5 (19.2)	3 (6.5)	1.82 (0.90-3.69)
18-59	**17** (23.6)	3 (11.5)	14 (30.4)	0.51 (0.17-1.58)
≥60	**35** (48.6)	12 (46.2)	23 (50.0)	1 [Reference]
Sex				
Female	**47** (65.3)	14 (53.8)	33 (71.7)	0.62 (0.34-1.13)
Male	**25** (34.7)	12 (46.2)	13 (28.3)	1 [Reference]
Race/ethnicity				
White	**59** (81.9)	23 (88.5)	36 (78.3)	1.69 (0.60-4.79)
American Indian	**13** (18.1)	3 (11.5)	10 (21.7)	1 [Reference]
Symptoms				
Diarrhea	**72** (100.0)	26 (100.0)	46 (100.0)	
Abdominal cramping	**72** (100.0)	26 (100.0)	46 (100.0)	
Blood visible in stools	**69** (95.8)	26 (100.0)	43 (93.5)	1.07 (0.99-1.15)
Subjective fever	**45** (62.5)	17 (65.4)	28 (60.9)	1.07 (0.75-1.54)
Nausea	**66** (94.3)[a]	25 (96.2)	41 (93.2)[a]	1.03 (0.92-1.15)
Vomiting[b]	**51 (70.8)**	**24 (92.3)**	**27 (58.7)**	**1.57 (1.20-2.05)**
Fatigue	**66** (94.3)[a]	23 (88.5)	43 (97.7)[a]	0.90 (0.78-1.05)
Headache	**31** (46.3)[c]	12 (48.0)[d]	19 (45.2)[e]	1.06 (0.63-1.80)
Body ache	**32** (47.8)[c]	11 (45.8)[a]	21 (48.8)[f]	0.94 (0.55-1.60)

Abbreviation: HUS, hemolytic uremic syndrome.
[a] Information missing for 2 persons.
[b] Boldfaced results indicate $P<.05$ for this row.
[c] Information missing for 5 persons.
[d] Information missing for 1 person.
[e] Information missing for 4 persons.
[f] Information missing for 3 persons.

coli O111 and had had close contact with a person who had consumed the restaurant food. Hospital medical records and outbreak investigation questionnaires were abstracted for demographics, previous use of medications, clinical presentation, laboratory results, treatment, and hospital course. Patients were excluded if the duration of hospitalization was less than 24 hours. Also excluded were patients without laboratory evidence of STEC infection who had an alternate explanatory diagnosis for their hospitalization (1 patient who was admitted for acute myocardial infarction).

STATISTICAL ANALYSIS

Risk ratios were calculated, and characteristics of patients with vs without HUS were compared using the 2-sided Wilcoxon rank sum test, 2-sided Fisher exact test, or Cochran-Mantel-Haenszel test wherever appropriate. Multivariate logistic regression analysis to determine factors associated with subsequent HUS was conducted in a backward stepwise fashion using variables significant in univariate analysis. For all statistical tests, $P<.05$ was considered significant. All analyses were performed using commercially available statistical software (SAS version 9.1; SAS Institute, Inc, Cary, North Carolina).

RESULTS

Overall, of 341 illnesses associated with the *E coli* O111 outbreak, 72 persons (21.1%) were hospitalized, representing 46.2% (72 of 156) of patients with confirmed or probable outbreak-associated *E coli* O111 infection. One adult patient (representing 1.4% of all those hospitalized) died. Among all hospitalized patients, 52 (72.2%) were adults 18 years or older, and 47 (65.3%) were female (**Table 2**); the median age was 56.5 years (age range, 1-88 years) (**Table 3**). Illness signs and symptoms and laboratory results for all hospitalized patients and for those with and without HUS are given in **Tables 2**, **3**, **4**, and **5**.

Twenty-six hospitalized persons (36.1%) were diagnosed as having HUS, accounting for 16.7% of 156 confirmed or probable *E coli* O111 infections in the overall outbreak and accounting for 7.6% of all 341 outbreak-related illnesses. Of 26 patients with HUS, 21 (80.8%) met criteria for confirmed HUS, and 5 (19.2%) met criteria for probable HUS; 15 (57.7%) of cases occurred among adults 18 years or older, and 14 (53.8%) were among female subjects (Table 2). The HUS attack rate among patients with confirmed or probable *E coli* infections from the overall outbreak varied by age group as follows: 25.0% (4 of 16) among children aged 0 to 4 years, 20.0% (2 of 10) among children aged 5 to 9 years, 41.7% (5 of 12) among persons aged 10 to 17 years, 5.8% (3 of 52) among persons aged 18 to 59 years, and 18.2% (12 of 66) among persons 60 years or older. The median time to HUS diagnosis was 6 days (range, 3-12 days) from the onset of diarrhea and 3 days (range, 0-7 days) after hospital admission. All patients with HUS reported diarrhea, abdominal cramping, and visible blood in stools. Patients with HUS did not differ from patients without HUS relative to the incubation period before the

Table 3. Characteristics of Hospitalized Patients and Their Illness in the 2008 *Escherichia coli* O111 Outbreak in Oklahoma[a]

Variable	All Hospitalized		HUS Cases		Non-HUS Cases		*P* Value[b]
	No.	Median (Range)	No.	Median (Range)	No.	Median (Range)	
Age, y	72	56.5 (1-88)	26	43.5 (1-88)	46	58.5 (1-88)	.23
Incubation period, d	66	4.0 (0-10)	24	4.0 (0-8)	42	4.0 (1-10)	.37
Maximum No. of stools in a 24-h period	65	10.0 (3-50)	23	12.0 (3-35)	42	10.0 (4-50)	.64
Diarrhea duration, d	63	6.0 (2-14)	20	7.0 (2-14)	43	6.0 (2-11)	.07
Days from diarrhea onset to admission	72	3.0 (0-9)	26	3.0 (0-7)	46	2.5 (0-9)	.48
White blood cell count at admission, /μL	**71**	**13 600 (5200-47 700)**	**26**	**16 400 (6200-47 700)**	**45**	**12 500 (5200-26 300)**	**.005**
Hemoglobin level at admission, g/dL	71	14.3 (7.7-18.2)	26	14.4 (10.9-18.2)	45	14.2 (7.7-17.5)	.98
Platelet count at admission, $\times 10^3$/μL	71	266 (44-462)	26	228 (44-412)	45	275.0 (168-462)	.07
Serum creatinine level at admission, mg/dL	**72**	**0.9 (0.2-4.6)**	**26**	**1.0 (0.4-4.6)**	**46**	**0.8 (0.2-1.7)**	**.01**
Serum urea nitrogen at admission, mg/dL	**71**	**13.0 (3-129)**	**26**	**17.0 (3-129)**	**45**	**12.0 (5-34)**	**.01**

Abbreviation: HUS, hemolytic uremic syndrome.

SI conversion factors: To convert creatinine level to micromoles per liter, multiply by 88.4; hemoglobin level to grams per liter, multiply by 10.0; platelet count to $\times 10^9$/L, multiply by 1.0; serum urea nitrogen level to millimoles per liter, multiply by 0.357; white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] $P < .05$ for boldfaced rows.

[b] Calculated using the 2-sided Wilcoxon rank sum test.

Table 4. Hospital Course in the 2008 *Escherichia coli* O111 Outbreak in Oklahoma[a]

Variable	All Hospitalized		HUS Cases		Non-HUS Cases		*P* Value[b]
	No.	Median (Range)	No.	Median (Range)	No.	Median (Range)	
Hospital days	**72**	**5.0 (1-55)**	**26**	**17.0 (3-55)**	**46**	**3.5 (1-36)**	**<.001**
Intensive care unit days	**72**	**0 (0-41)**	**26**	**7.5 (0-41)**	**46**	**0 (0-15)**	**<.001**
Dialysis treatments	18	6.0 (1-31)	17	6.0 (1-31)	1	12.0 (12)	.40
Days on dialysis	18	9.5 (1-27)	17	9.0 (1-25)	1	27.0 (27)	.14
Maximum white blood cell count, /μL	**72**	**16 400 (5200-51 600)**	**26**	**24 700 (10 100-51 600)**	**46**	**13 800 (5200-26 300)**	**<.001**
Minimum hemoglobin level, g/dL	**72**	**11.2 (5.1-15.4)**	**26**	**7.4 (5.1-12.2)**	**46**	**11.8 (7.7-15.4)**	**<.001**
Minimum platelet count, $\times 10^3$/μL	**72**	**180.0 (11-444)**	**26**	**31.5 (11-139)**	**46**	**216.0 (61-444)**	**<.001**
Maximum serum creatinine level, mg/dL	**72**	**1.1 (0.2-8.3)**	**26**	**3.7 (1.0-8.3)**	**46**	**0.8 (0.2-7.1)**	**<.001**

Abbreviation: HUS, hemolytic uremic syndrome.

SI conversion factors: To convert creatinine level to micromoles per liter, multiply by 88.4; hemoglobin level to grams per liter, multiply by 10.0; platelet count to $\times 10^9$/L, multiply by 1.0; white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] $P < .05$ for boldfaced rows.

[b] Calculated using the 2-sided Wilcoxon rank sum test.

onset of diarrhea, days from diarrhea onset to admission, maximum number of stools in a 24-hour period, or diarrhea duration (Table 3) or relative to the presence of subjective fever, headache, fatigue, body ache, or nausea (Table 2). However, patients with HUS were more likely than patients without HUS to experience vomiting (Table 2) and to have documented fever during their hospital stay (Table 5).

Univariate analysis identified several factors that were statistically different between patients with vs without HUS at the time of admission; patients with HUS had higher white blood cell (WBC) counts and serum creatinine and serum urea nitrogen levels (Table 3 and **Table 6**) and had higher proportions with vomiting before hospital admission (Table 6). Neither hemoglobin level or platelet count (Table 3) nor the presence of proteinuria or hematuria (Table 6) at the time of admission was significantly different between patients with vs without HUS. In multivariate analysis, the following admission variables were independently associated with HUS development and were included in the final model: WBC count of at least 20 000 /μL (adjusted odds ratio [aOR], 11.3; 95% confidence interval [CI], 1.7-75.3), elevated serum creatinine level for age (9.7; 1.4-69.2), and vomiting before hospital admission (6.8; 1.5-31.3) (to convert WBC count to $\times 10^9$/L, multiply by 0.001) (**Table 7**).

Fifteen patients with HUS (57.7%) received antimicrobial agents after the onset of symptoms but before the diagnosis of HUS, and 27 patients without HUS (58.7%) received antimicrobial agents during their illness (risk ratio [RR], 1.0; 95% CI, 0.5-1.8) (Table 6). No difference between groups by antimicrobial use was detected when adjusting for severity of illness using admission WBC count of at least 20 000 /μL as a proxy for more severe illness. Likewise, administration of antimotility agents (eg, diphenoxylate hydrochloride or loperamide hydrochloride) (RR, 1.7; 95% CI, 0.9-3.0) or any drug with antimotility effects (eg, the aforementioned agents plus medications that decrease peristalsis [eg, opioid analgesics]) also did not differ between groups (1.4; 0.6-2.9). Receipt of antacid medication, antipyretics, nonsteroidal anti-inflammatory agents, or corticosteroids before hospital admission did not vary by HUS status (data not shown).

Patients with HUS had significantly longer hospital stays and more days in the intensive care unit than patients without HUS (Table 4). Patients with HUS were

Table 5. Hospital Findings of Patients in the 2008 *Escherichia coli* O111 Outbreak in Oklahoma[a]

Finding	No./Total No. (%)			Risk Ratio (95% Confidence Interval)
	All Hospitalized	HUS Cases	Non-HUS Cases	
Documented fever, temperature >38.0°C	**16/72 (22.2)**	**11/26 (42.3)**	**5/46 (10.9)**	**3.89 (1.52-9.98)**
Tachycardia, heart rate >100 beats/min in person aged >12 y	**20/55 (36.4)**	**11/17 (64.7)**	**9/38 (23.7)**	**2.73 (1.40-5.34)**
Hypotension, SBP <100 mm Hg in person aged >12 y	**16/55** (29.1)	7/17 (41.2)	9/38 (23.7)	1.74 (0.78-3.89)
Vasopressor support required	**5/72** (6.9)	4/26 (15.4)	1/45 (2.2)	7.08 (0.83-60.02)
Acute hypertension, SBP >140 mm Hg and no past hypertension	**21/39 (53.8)**	**12/15 (80.0)**	**9/24 (37.5)**	**2.13 (1.20-3.79)**
Infiltrate on chest imaging	**23/39 (59.0)**	**18/23 (78.3)**	**5/16 (31.3)**	**2.50 (1.17-5.34)**
Pleural effusion	**18/38 (47.4)**	**16/22 (72.7)**	**2/16 (12.5)**	**5.82 (1.55-21.81)**
Pericardial effusion	**4/8** (50.0)	4/5 (80.0)	0/3	6.00 (0.43-83.54)
Peripheral edema	**18/71 (25.4)**	**16/26 (61.5)**	**2/45 (4.4)**	**13.85 (3.45-55.50)**
Pancreatic enzyme elevation, lipase or amylase level >200 U/L	**8/72 (11.1)**	**7/26 (26.9)**	**1/46 (2.2)**	**12.38 (1.61-95.18)**
Altered consciousness	**17/72 (23.6)**	**12/26 (46.2)**	**5/46 (10.9)**	**4.25 (1.68-10.72)**
Seizure activity	**3/72** (4.2)	3/26 (11.5)	0/46	12.18 (0.65-227.09)
Any neurologic abnormality	**19/72 (26.4)**	**14/26 (53.8)**	**5/46 (10.9)**	**4.95 (2.01-12.19)**
Dialysis	**18/72 (25.0)**	**17/26 (65.4)**	**1/46 (2.2)**	**30.08 (4.24-213.23)**
Transfusion	**23/72 (31.9)**	**21/26 (80.8)**	**2/46 (4.3)**	**18.58 (4.73-72.99)**
Plasmapheresis	**8/72 (11.1)**	**8/26 (30.8)**	**0/46**	**29.59 (1.78-492.82)**
Mechanical ventilation	**9/72 (12.5)**	**8/26 (30.8)**	**1/46 (2.2)**	**14.20 (1.87-106.96)**
Shiga toxin positive, EHEC EIA or STX PCR	**35/55** (63.6)	14/21 (66.7)	21/34 (61.8)	1.08 (0.72-1.61)
Escherichia coli O111 isolated	**31/72** (43.1)	12/26 (46.2)	19/46 (41.3)	1.12 (0.65-1.92)

Abbreviations: EHEC, enterohemorrhagic *E coli;* EIA, enzyme-linked immunoassay; HUS, hemolytic uremic syndrome; PCR, polymerase chain reaction; SBP, systolic blood pressure; STX, Shiga toxin–encoding gene.

SI conversion factor: To convert amylase and lipase levels to microkatals per liter, multiply by 0.0167.

[a] $P<.05$ for boldfaced rows.

Table 6. Univariate Hospital Admission Variables and Subsequent Diagnosis of Hemolytic Uremic Syndrome in the 2008 *Escherichia coli* O111 Outbreak in Oklahoma[a]

Variable	No. (%)			Risk Ratio (95% Confidence Interval)
	All Hospitalized (n=72)	HUS Cases (n=26)	Non-HUS Cases (n=46)	
White blood cell count ≥20 000 /μL, reference <20 000 /μL	**12 (16.9)**[b]	**10 (38.5)**	**2 (4.4)**[b]	**3.07 (1.88-5.01)**
Elevated creatinine level for age, reference normal level	**11 (15.3)**	**9 (34.6)**	**2 (4.3)**	**2.94 (1.80-4.79)**
Serum urea nitrogen level >30 mg/dL, reference ≤30 mg/dL	**10 (14.1)**[b]	**8 (30.8)**	**2 (4.4)**[b]	**2.71 (1.65-4.45)**
Vomiting before hospital admission, reference none	**48 (66.7)**	**23 (88.5)**	**25 (54.3)**	**3.83 (1.28-11.50)**
Proteinuria, reference none	**20** (27.8)	9 (34.6)	11 (23.9)	1.38 (0.74-2.56)
Hematuria, reference none	**20** (27.8)	8 (30.8)	12 (26.1)	1.16 (0.60-2.22)
Previous antimicrobial use, reference none[c]	**42** (58.3)	15 (57.7)	27 (58.7)	0.97 (0.52-1.81)
Previous antimotility agent use, reference none[d]	**22** (30.6)	11 (42.3)	11 (23.9)	1.67 (0.92-3.02)
Previous use of any drug with antimotility effects, reference none[e]	**51** (70.8)	20 (76.9)	31 (67.4)	1.37 (0.64-2.93)

Abbreviation: HUS, hemolytic uremic syndrome.

SI conversion factors: To convert urea nitrogen level to millimoles per liter, multiply by 0.357; white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] $P<.05$ for boldfaced rows.

[b] Information missing for 1 person.

[c] Antimicrobial agents administered after the onset of symptoms and before the diagnosis of HUS for patients with HUS and at any time during hospitalization for patients without HUS.

[d] Antimotility agents (eg, loperamide hydrochloride, diphenoxylate hydrochloride, and dicyclomine hydrochloride) administered after the onset of symptoms and before the diagnosis of HUS for patients with HUS and at any time during hospitalization for patients without HUS.

[e] Medications with antimotility effects (eg, antimotility agents plus opioid analgesics) administered after the onset of symptoms and before the diagnosis of HUS for patients with HUS and at any time during hospitalization for patients without HUS.

also more likely to exhibit signs of serious illness—eg, acutely elevated blood pressure (among those with no history of hypertension), lung infiltrate or pleural effusion on chest imaging, altered level of consciousness, or any previously undiagnosed neurologic sign—and to require supportive procedures such as mechanical ventilation; 17 of patients with HUS required dialysis (65.4%), and 21 received transfusion of red blood cells, platelets, or fresh frozen plasma (80.8%) (Table 5). Neurologic signs among patients with HUS included confusion, disorientation, agitation, seizures, myoclonic jerking, short-term memory deficits, expressive aphasia, vertigo, diplopia, and asymmetric facial weakness.

Although hemoglobin level and platelet counts at admission were not statistically different between the 2 groups, patients with HUS subsequently had significantly lower minimum hemoglobin levels and platelet counts during hospitalization than patients without HUS (Table 4). Red blood cell fragmentation developed on peripheral blood smear in 80.8% (21 of 26) of patients with

Table 7. Final Multivariate Model of Hospital Admission Variables and Subsequent Diagnosis of Hemolytic Uremic Syndrome in the 2008 *Escherichia coli* O111 Outbreak in Oklahoma

Variable	Adjusted Odds Ratio (95% Confidence Interval)[a]
White blood cell count ≥20 000 /μL	11.3 (1.7-75.3)
Elevated serum creatinine level for age	9.7 (1.4-69.2)
Vomiting before hospital admission	6.8 (1.5-31.3)

SI conversion factor: To convert white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] $P < .05$ for all.

HUS. The median time from diarrhea onset to appearance of fragments on blood smear was 7 days; the minimum platelet count occurred at 7.5 days, and the minimum hemoglobin level occurred at 11.5 days. The maximum WBC count was attained at a median of 5.5 days after diarrhea onset and measured at least 20 000 /μL in 69.2% of patients with HUS compared with 8.7% of patients without HUS. Hematuria was detected in specimens from 21 of 24 patients with HUS (87.5%) and proteinuria in 22 of 24 patients with HUS (91.7%). Proteinuria first appeared a median of 5 days after the onset of diarrhea and hematuria at a median of 6 days.

Neither Shiga toxin detection nor isolation of *E coli* O111 was significantly more likely in samples from patients with vs without HUS (Table 5). Among those with any laboratory screening for STEC, 14 of 21 specimens (66.7%) from HUS cases were positive. Specifically, polymerase chain reaction for Shiga toxin genes was positive in 10 of 14 (71.4%) specimens from HUS cases, and 13 of 21 (61.9%) were positive on enzyme-linked immunoassay for STEC. In addition, *E coli* O111 was isolated in specimens from 46.2% of all 26 patients with HUS. Among specimens with positive culture for *E coli* O111 that also had polymerase chain reaction testing for Shiga toxin genes, all specimens (10 of 10) from HUS cases and 94.4% (17 of 18) of specimens from patients without HUS had both *stx1* and *stx2* genes detected.

In all, 23 patients with HUS (88.5%) were discharged home, 2 (7.7%) required ongoing care in a rehabilitation or skilled nursing facility, and 1 (3.8%) died. Eight patients with HUS (30.8%) were discharged from the hospital having a new diagnosis of hypertension, and 2 (7.7%) had a new neurologic deficit. Ongoing requirement for dialysis at hospital discharge was noted in 2 patients with HUS (7.7%).

COMMENT

In August 2008, Oklahoma experienced the largest outbreak of *E coli* O111 recorded in the United States. Documented were 341 illnesses, 72 hospitalizations, and 1 death resulting from this restaurant-associated outbreak. Twenty-six persons, all of whom were hospitalized, were diagnosed as having HUS, and 65.4% of patients with HUS required dialysis. Unlike in many STEC outbreaks, the highest proportions of patients with *E coli* O111 outbreak-related hospitalizations and HUS diagnoses were adults 18 years or older. Previously described STEC infections and HUS have primarily involved children, particularly the youngest age groups.[1,4,6,17-22] However, in the outbreak reported herein, the highest HUS attack rates occurred among older children (age range, 10-17 years), and almost three-quarters of hospitalized persons and more than one-half of patients with HUS were adults. In a review of isolates sent to the Centers for Disease Control and Prevention between 1983 and 2002 for serotyping, 57% of non-O157 serotypes isolated were from persons 10 years or older.[7] Whether propensity for illness to occur among a high proportion of older age groups is a characteristic of non-O157 STEC serotypes, STEC O111 specifically, or is merely a function of the exposure setting is unknown. Retail foodborne outbreaks likely reflect the age distribution of the consumers. In Australia in 1995, patients with HUS from an *E coli* O111 outbreak associated with fermented sausage were significantly older, and the proportion of children younger than 5 years was lower than that of patients with HUS from sporadic non-O157 infections, possibly reflecting that younger children were less likely to consume the type of food implicated.[9] Similarly, in an outbreak of *E coli* O111 at a cheerleading camp, the median age of ill persons was 16 years, reflecting the predominant age group of exposed persons.[14] The O111 outbreak presented herein demonstrates that, at least in certain outbreak settings, many older children and adults can contract non-O157 STEC infection and HUS.

Studies[18,20,21,23-27] have reported that non-O157 STEC illness is less severe than O157 illness based on the finding that patients are less likely to report bloody diarrhea or experience HUS. However, in the Centers for Disease Control and Prevention serotype study,[7] STEC O111 was the only non-O157 serotype that was statistically associated with HUS and accounted for approximately 50% of non-O157 STEC–related HUS. In the present O111 outbreak, all patients with HUS had visible blood in stools, and the HUS attack rate (16.7%) was similar to the HUS attack rates reported in *E coli* O157 infections (2%-15%).[4-6,17,19,24,26,28-30] Compared with outbreaks related to other STEC serotypes,[6,17,26,31-33] the proportion of complications among patients with HUS was substantial in our investigation, with 65.4% (17 of 26) requiring dialysis, 80.0% (12 of 15) having acute hypertension, more than 70% having chest infiltrates (18 of 23, 78.3%) or pleural effusions (16 of 22, 53.8%), and 53.8% having any neurologic abnormality. Central nervous system manifestations such as seizures, hemiparesis, stupor, or coma have been reported in one-quarter of patients with HUS,[18,20-22,28,33] approximately one-quarter have pulmonary consequences such as pleural effusion,[28] and one-fifth to two-thirds experience acute hypertension.[20,22,28] A high proportion of neurologic manifestations (75%) was also reported in an Italian HUS outbreak in which *E coli* O111 was implicated.[10] Data presented herein indicate that, compared with O157-related HUS, HUS caused by STEC O111 has a similar attack rate and proportion of patients with bloody stools and a similar or higher rate of acute complications.

In addition to describing *E coli* O111–associated illness and HUS from this outbreak, we sought to determine signs on admission that are associated with im-

pending HUS. Factors on admission that were discovered in our multivariate model to be significantly associated with subsequent HUS included WBC count of at least 20 000 /μL, serum creatinine level elevated for age, and vomiting before hospital admission. Elevated initial WBC count[3,4,6,19,22,29,34,35] and vomiting[19] have been previously identified as potential predictors of HUS caused by *E coli* O157. However, unlike previous studies,[3,6,22,36] neither age nor sex was significantly associated with HUS diagnosis in this investigation. Because early recognition of HUS and timely appropriate treatment have been associated with better outcomes,[37] clinicians can potentially use these characteristics to identify patients at risk for HUS and provide early aggressive supportive care. Further evaluation is needed to determine if the identified factors at the time of admission are truly predictive of subsequent HUS diagnosis.

Results of some studies[29,34] have indicated that antibiotics should not be administered to patients experiencing possible STEC-related illness because of increased risk for developing HUS. Other investigators have discovered a protective effect with correct antibiotic use.[36] A meta-analysis[38] of 26 studies addressing antibiotic therapy for *E coli* O157 infections observed no association with higher risk for HUS. It has also been suggested that the use of antibiotics might be an indicator of disease severity[4,39] rather than a cause of HUS. Similarly, investigators in some studies[19,33,36] have recommended that antimotility agents should not be administered in the setting of suspected STEC, but Cimolai et al[36] observed no association with HUS associated with short-term use of antimotility agents. In the investigation presented herein, prior use of antimicrobial agents, antimotility agents, or medications with antimotility adverse effects was not significantly associated with subsequent HUS diagnosis. These findings might be limited to the particular outbreak strain of O111; other STEC strains might respond differently to antibiotic exposure or to agents that reduce gastrointestinal motility.

It is apparent from this outbreak and from preceding US outbreaks that *E coli* O111 is capable of causing serious disease among humans and might be emerging in the United States or at least is present to a greater extent than was previously appreciated. STEC O111 was first reported in North America in 1990 among an Ohio family cluster.[13] Since then, O111 STEC outbreaks have been reported at a 1999 cheerleading camp in Texas,[14,15] among attendees of a farm day camp between 2000 and 2001 in Minnesota,[40] and in New York in 2004 (associated with consumption of unpasteurized apple cider).[16] Non-O157 STEC might be underrecognized as a cause of gastrointestinal illness because routine laboratory practices often do not screen for these pathogens. In a 2007 Connecticut study,[27] only 31% of clinical laboratories in the state had conducted immunoassays for Shiga toxin. A special prevalence study[41] of STEC in Nebraska in 1998 identified 2 indistinguishable STEC O111 isolates collected 1 day apart from different patients in the same community, suggesting that an outbreak of STEC O111 might have occurred that was undetected by standard laboratory protocols. In the Nebraska study, non-O157 isolates were as prevalent as O157 serogroups. Greater vigilance is needed in testing for non-O157 STEC among patients experiencing diarrheal illness or HUS to better estimate the true incidence of these pathogens.

This study had certain limitations. As a retrospective study, we were limited by the accuracy and completeness of available medical records. Also, documentation, laboratory testing, and therapy varied among patients managed by different physicians and allied health professionals and different facilities, disallowing uniformity. The number of outbreak-related hospitalizations in the cohort was limited and might not have been an adequate sample size to detect differences that might actually exist between groups. Last, because this analysis is based only on hospitalized patients and used outbreak-specific case definitions, results cannot be extrapolated to nonhospitalized persons or to other outbreaks.

Future studies of O111-associated outbreaks are needed to further characterize this serotype, but in this evaluation of hospitalized patients, illness caused by the outbreak strain of *E coli* O111 seems to match or exceed the severity of its counterpart O157. Clinicians should be aware that certain serotypes of non-O157 STEC can cause severe illness (including HUS) and that HUS can occur among adults as well as children. Although children are classically considered at greatest risk for HUS, patients of all ages with suspected STEC infection should be monitored carefully for early signs of impending HUS. Non-O157 STEC should be considered as possible causative organisms in outbreaks of gastrointestinal illness, particularly when bloody diarrhea and severe abdominal cramping or HUS is present. Identification and national reporting can improve our estimate of the burden of disease caused by non-O157 STEC and should provide opportunities for epidemiologic investigation to better understand the spectrum of disease caused by these pathogens.

Accepted for Publication: March 8, 2010.
Correspondence: Emily W. Piercefield, MD, DVM, MS, MPH, Epidemic Intelligence Service Program, Scientific Education and Professional Development Program Office, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mail Stop E-92, Atlanta, GA 30333 (epiercefield@cdc.gov).
Author Contributions: Dr Piercefield had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Piercefield, Bradley, Coffman, and Mallonee. *Acquisition of data*: Piercefield and Coffman. *Analysis and interpretation of data*: Piercefield, Bradley, Coffman, and Mallonee. *Drafting of the manuscript*: Piercefield. *Critical revision of the manuscript for important intellectual content*: Piercefield, Bradley, Coffman, and Mallonee. *Statistical analysis*: Piercefield. *Obtained funding*: Bradley and Mallonee. *Administrative, technical, or material support*: Piercefield, Coffman, Bradley, and Mallonee. *Study supervision*: Piercefield, Coffman, Bradley, and Mallonee.
Financial Disclosure: None reported.
Funding/Support: This study was supported by the Oklahoma State Department of Health.
Disclaimer: The findings and conclusions of this study are those of the authors and do not necessarily repre-

sent the official position of the Centers for Disease Control and Prevention.

Previous Presentations: This study was presented at the 2009 Council of State and Territorial Epidemiologists Annual Conference; June 8, 2009; Buffalo, New York; and at the 58th Annual Epidemic Intelligence Service of the Centers for Disease Control and Prevention; April 21, 2009; Atlanta, Georgia; and is published after peer review and revision.

Additional Contributions: Julie M. Magri, MD, Patricia M. Griffin, MD, Samir V. Sodha, MD, and L. Hannah Gould, MD, gave helpful advice during the preparation of presentations and reports related to the HUS investigation. The Oklahoma State Department of Health participated in extensive investigation. The Oklahoma State Public Health Laboratory and the Enteric Diseases Laboratory Branch at the Centers for Disease Control and Prevention were responsible for identifying and characterizing the organism involved in the outbreak. We thank the medical records personnel at various hospitals for their help in the investigation.

REFERENCES

1. McNabb SJ, Jajosky RA, Hall-Baker PA, et al; Centers for Disease Control and Prevention (CDC). Summary of notifiable diseases: United States, 2006. *MMWR Morb Mortal Wkly Rep*. 2008;55(53):1-92.
2. Mead PS, Slutsker L, Dietz V, et al. Food-related illness and death in the United States. *Emerg Infect Dis*. 1999;5(5):607-625.
3. Dundas S, Todd WT, Stewart AI, Murdoch PS, Chaudhuri AK, Hutchinson SJ. The central Scotland *Escherichia coli* O157:H7 outbreak: risk factors for the hemolytic uremic syndrome and death among hospitalized patients. *Clin Infect Dis*. 2001;33(7):923-931.
4. Griffin PM, Tauxe RV. The epidemiology of infections caused by *Escherichia coli* O157:H7, other enterohemorrhagic *E. coli*, and the associated hemolytic uremic syndrome. *Epidemiol Rev*. 1991;13:60-98.
5. Rangel JM, Sparling PH, Crowe C, Griffin PM, Swerdlow DL. Epidemiology of *Escherichia coli* O157:H7 outbreaks, United States, 1982-2002. *Emerg Infect Dis*. 2005;11(4):603-609.
6. Tserenpuntsag B, Chang HG, Smith PF, Morse DL. Hemolytic uremic syndrome risk and *Escherichia coli* O157:H7. *Emerg Infect Dis*. 2005;11(12):1955-1957.
7. Brooks JT, Sowers EG, Wells JG, et al. Non-O157 Shiga toxin–producing *Escherichia coli* infections in the United States, 1983-2002. *J Infect Dis*. 2005;192(8):1422-1429.
8. Centers for Disease Control and Prevention (CDC). Community outbreak of hemolytic uremic syndrome attributable to *Escherichia coli* O111:NM: South Australia 1995. *MMWR Morb Mortal Wkly Rep*. 1995;44(29):550-551, 557-558.
9. Elliott EJ, Robins-Browne RM, O'Loughlin EV, et al; Contributors to the Australian Paediatric Surveillance Unit. Nationwide study of haemolytic uraemic syndrome: clinical, microbiological, and epidemiological features. *Arch Dis Child*. 2001;85(2):125-131.
10. Caprioli A, Luzzi I, Rosmini F, et al. Community-wide outbreak of hemolytic-uremic syndrome associated with non-O157 verocytotoxin-producing *Escherichia coli*. *J Infect Dis*. 1994;169(1):208-211.
11. Morabito S, Karch H, Mariani-Kurkdjian P, et al. Enteroaggregative, Shiga toxin–producing *Escherichia coli* O111:H2 associated with an outbreak of hemolytic-uremic syndrome. *J Clin Microbiol*. 1998;36(3):840-842.
12. Bettelheim KA. The non-O157 Shiga-toxigenic (verocytotoxigenic) *Escherichia coli*: under-rated pathogens. *Crit Rev Microbiol*. 2007;33(1):67-87.
13. Banatvala N, Debeukelaer MM, Griffin PM, et al. Shiga-like toxin–producing *Escherichia coli* O111 and associated hemolytic-uremic syndrome: a family outbreak. *Pediatr Infect Dis J*. 1996;15(11):1008-1011.
14. Centers for Disease Control and Prevention. *Escherichia coli* O111:H8 outbreak among teenage campers: Texas, 1999. *JAMA*. 2000;283(19):2517-2518.
15. Brooks JT, Bergmire-Sweat D, Kennedy M, et al. Outbreak of Shiga toxin–producing *Escherichia coli* O111:H8 infections among attendees of a high school cheerleading camp. *Clin Infect Dis*. 2004;38(2):190-198.
16. Vojdani JD, Beuchat LR, Tauxe RV. Juice-associated outbreaks of human illness in the United States, 1995 through 2005. *J Food Prot*. 2008;71(2):356-364.
17. Heymann DL. *Control of Communicable Diseases Manual*. 19th ed. Washington, DC: American Public Health Association; 2008.
18. Banatvala N, Griffin PM, Greene KD, et al; Hemolytic Uremic Syndrome Study Collaborators. The United States National Prospective Hemolytic Uremic Syndrome Study: microbiologic, serologic, clinical, and epidemiologic findings. *J Infect Dis*. 2001;183(7):1063-1070.
19. Bell BP, Griffin PM, Lozano P, Christie DL, Kobayashi JM, Tarr PI. Predictors of hemolytic uremic syndrome in children during a large outbreak of *Escherichia coli* O157:H7 infections. *Pediatrics*. 1997;100(1):E12.
20. Gerber A, Karch H, Allerberger F, Verweyen HM, Zimmerhackl LB. Clinical course and the role of Shiga toxin–producing *Escherichia coli* infection in the hemolytic-uremic syndrome in pediatric patients, 1997-2000, in Germany and Austria: a prospective study. *J Infect Dis*. 2002;186(4):493-500.
21. Scheiring J, Andreoli SP, Zimmerhackl LB. Treatment and outcome of Shiga-toxin–associated hemolytic uremic syndrome (HUS). *Pediatr Nephrol*. 2008;23(10):1749-1760.
22. Siegler RL, Pavia AT, Christofferson RD, Milligan MK. A 20-year population-based study of postdiarrheal hemolytic uremic syndrome in Utah. *Pediatrics*. 1994;94(1):35-40.
23. Jelacic JK, Damrow T, Chen GS, et al. Shiga toxin–producing *Escherichia coli* in Montana: bacterial genotypes and clinical profiles. *J Infect Dis*. 2003;188(5):719-729.
24. Klein EJ, Stapp JR, Clausen CR, et al. Shiga toxin–producing *Escherichia coli* in children with diarrhea: a prospective point-of-care study. *J Pediatr*. 2002;141(2):172-177.
25. Werber D, Behnke SC, Fruth A, et al. Shiga toxin–producing *Escherichia coli* infection in Germany: different risk factors for different age groups. *Am J Epidemiol*. 2007;165(4):425-434.
26. Tarr PI, Gordon CA, Chandler WL. Shiga-toxin–producing *Escherichia coli* and haemolytic uraemic syndrome. *Lancet*. 2005;365(9464):1073-1086.
27. Centers for Disease Control and Prevention (CDC). Laboratory-confirmed non-O157 Shiga toxin–producing *Escherichia coli*: Connecticut, 2000-2005. *MMWR Morb Mortal Wkly Rep*. 2007;56(2):29-31.
28. Brandt JR, Fouser LS, Watkins SL, et al. *Escherichia coli* O 157:H7–associated hemolytic-uremic syndrome after ingestion of contaminated hamburgers. *J Pediatr*. 1994;125(4):519-526.
29. Wong CS, Brandt JR. Risk of hemolytic uremic syndrome from antibiotic treatment of *Escherichia coli* O157:H7 colitis. *JAMA*. 2002;288(24):3112.
30. Cody SH, Glynn MK, Farrar JA, et al. An outbreak of *Escherichia coli* O157:H7 infection from unpasteurized commercial apple juice. *Ann Intern Med*. 1999;130(3):202-209.
31. Mark Taylor C. Enterohaemorrhagic *Escherichia coli* and *Shigella dysenteriae* type 1–induced haemolytic uraemic syndrome. *Pediatr Nephrol*. 2008;23(9):1425-1431.
32. Paton JC, Paton AW. Pathogenesis and diagnosis of Shiga toxin–producing *Escherichia coli* infections. *Clin Microbiol Rev*. 1998;11(3):450-479.
33. Boyce TG, Swerdlow DL, Griffin PM. *Escherichia coli* O157:H7 and the hemolytic-uremic syndrome. *N Engl J Med*. 1995;333(6):364-368.
34. Pavia AT, Nichols CR, Green DP, et al. Hemolytic-uremic syndrome during an outbreak of *Escherichia coli* O157:H7 infections in institutions for mentally retarded persons: clinical and epidemiologic observations. *J Pediatr*. 1990;116(4):544-551.
35. Ikeda K, Ida O, Kimoto K, Takatorige T, Nakanishi N, Tatara K. Predictors for the development of haemolytic uraemic syndrome with *Escherichia coli* O157:H7 infections: with focus on the day of illness. *Epidemiol Infect*. 2000;124(3):343-349.
36. Cimolai N, Carter JE, Morrison BJ, Anderson JD. Risk factors for the progression of *Escherichia coli* O157:H7 enteritis to hemolytic-uremic syndrome. *J Pediatr*. 1990;116(4):589-592.
37. Garg AX, Suri RS, Barrowman N, et al. Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression. *JAMA*. 2003;290(10):1360-1370.
38. Safdar N, Said A, Gangnon RE, Maki DG. Risk of hemolytic uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 enteritis: a meta-analysis. *JAMA*. 2002;288(8):996-1001.
39. Carter AO, Borczyk AA, Carlson JA, et al. A severe outbreak of *Escherichia coli* O157:H7–associated hemorrhagic colitis in a nursing home. *N Engl J Med*. 1987;317(24):1496-1500.
40. Smith KE, Stenzel SA, Bender JB, et al. Outbreaks of enteric infections caused by multiple pathogens associated with calves at a farm day camp. *Pediatr Infect Dis J*. 2004;23(12):1098-1104.
41. Fey PD, Wickert RS, Rupp ME, Safranek TJ, Hinrichs SH. Prevalence of non-O157:H7 Shiga toxin–producing *Escherichia coli* in diarrheal stool samples from Nebraska. *Emerg Infect Dis*. 2000;6(5):530-533.