Hemolytic-Uremic Syndrome and Escherichia coli O121 at a Lake in Connecticut, 1999

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ABSTRACT. Objective. Non-O157 Shiga toxin-producing Escherichia coli (STEC) have emerged as an important public health problem. Outbreaks attributed to non-O157 STEC rarely are reported. In 1999, follow-up of routine surveillance reports of children with hemolytic-uremic syndrome (HUS) identified a small cluster of 3 cases of HUS, all of whom had spent overlapping time in a Connecticut lake community in the week before onset of symptoms. We conducted an investigation to determine the magnitude and source of the outbreak and to determine risk factors associated with the transmission of illness.

Methods. We conducted a cohort study and an environmental investigation. The study population included all people who were at the lake in a defined geographic area during July 16–25, 1999. This time and area were chosen on the basis of interviews with the 3 HUS case-patients. A case was defined as diarrhea (≥3 loose stools/d for ≥3 days) in a person who was at the lake during July 16–25, 1999. Stool samples were requested from any lake resident with diarrheal illness. Stools were cultured for Salmonella, Shigella, Campylobacter, and E coli O157. Broth cultures of stools were tested for Shiga toxin. Case-patients were asked to submit a serum specimen for antibody testing to lipopolysaccharides of selected STEC. Environmental samples from sediment, drinking water, lake water, and ice were obtained and cultured for E coli and tested for Shiga toxin. An environmental evaluation of the lake was conducted to identify any septic, water supply system, or other environmental condition that could be related to the outbreak.

Results. Information was obtained for 436 people from 165 (78%) households. Eleven (2.5%) people had illnesses that met the case definition, including the 3 children with HUS. The attack rate was highest among those who were younger than 10 years and who swam in the lake on July 17 or 18 (12%; relative risk [RR]: 7.3). Illness was associated with swimming (RR = 8.3) and with swallowing water while swimming (RR = 7.0) on these days. No person who swam only after July 18 developed illness. Clinical characteristics of case-patients included fever (27%), bloody diarrhea (27%), and severe abdominal cramping (73%). Only the 3 children with HUS required hospitalization. No bacterial pathogen was isolated from the stool of any case-patient. Among lake residents outside the study area, E coli O121:H19 was obtained from a Shiga toxin–producing isolate from a toddler who swam in the lake. Serum was obtained from 7 of 11 case-patients. Six of 7 case-patients had E coli O121 antibody titers that ranged from 1:320 to >1:20 480. E coli indicative of fecal contamination was identified from sediment and water samples taken from a storm drain that emptied into the beach area and from a stream bed located between 2 houses, but no Shiga toxin–producing strain was identified.

Conclusions. Our findings are consistent with a transient local beach contamination in mid-July, probably with E coli O121:H19, which seems to be able to cause severe illness. Without HUS surveillance, this outbreak may have gone undetected by public health officials. This outbreak might have been detected sooner if Shiga toxin screening had been conducted routinely in HUS cases. Laboratory testing that relies solely on the inability of an isolate to ferment sorbitol will miss non-O157 STEC, such as E coli O121. Serologic testing can be used as an adjunct in the diagnosis of STEC infections. Lake-specific recommendations included education, frequent water sampling, and alternative means for toddlers to use lake facilities. Pediatrics 2001;108(4). URL: http://www.pediatrics.org/cgi/content/full/108/4/e59; Shiga toxin–producing E coli, enterohemorrhagic E coli, hemolytic uremic syndrome, gastroenteritis.

ABBREVIATIONS. STEC, Shiga toxin–producing Escherichia coli; CDC, Centers for Disease Control and Prevention; HUS, hemolytic-uremic syndrome; DPH, Department of Public Health; RR, relative risk; SMAC, sorbitol-MacConkey agar; EHEC, enterohemorrhagic Escherichia coli; ELISA, enzyme-linked immunosorbent assay; LPS, lipopolysaccharides; IgM, immunoglobulin M; IgG, immunoglobulin G.

Infections with Shiga toxin–producing bacteria are an important public health problem. Escherichia coli O157:H7 is the most common Shiga toxin–producing E coli (STEC) in the United States. E coli O157:H7 initially was recognized as a human pathogen in 1982 during outbreaks of diarrhea associated with the consumption of contaminated ground beef at fast-food restaurants in Oregon and Michigan. Since then, E coli O157 has been associated with other foods, water, and person-to-person transmission. In
the United States, *E coli* O157 is responsible for an estimated 73,000 illnesses annually.2 The number of *E coli* O157 outbreaks reported to the Centers for Disease Control and Prevention (CDC) has increased from <5 in 1983 to >35 in 1999.3,4

*E coli* O157:H7 is the most common pathogen associated with postdiarrheal hemolytic-uremic syndrome (HUS) in the United States. HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and azotemia and is the most frequent cause of acute renal failure in children. The annual incidence of HUS in the United States is approximately 3 cases per 100,000 population among children who are younger than 5 years. Approximately 5% to 10% of people with diarrhea caused by *E coli* O157:H7 develop HUS. The mortality rate among children with HUS is 3% to 5%.5,6

Although researchers have learned much regarding the clinical spectrum of disease, modes of transmission, and long-term sequelae of *E coli* O157:H7, little is known about non-O157 STEC infection. Non-O157 STEC usually are recognized only when specialized testing is performed in the setting of investigations of HUS or diarrheal outbreaks.7–10 Historically, standard laboratory testing for *E coli* O157 has not detected non-O157 STEC. Most *E coli* O157 do not ferment sorbitol within 24 hours, allowing for easy screening if specimens are collected within a week of onset of diarrhea. Most non-O157 STEC are sorbitol fermenters, leaving them without an easily discernible biochemical marker. Screening for Shiga toxin production in broth cultures is an important way to identify non-O157 STEC and does not require the presence of viable organisms.

HUS has been a reportable disease in Connecticut since 1994. On July 30, 1999, a pediatric nephrologist notified the Connecticut Department of Public Health (DPH) of a case of HUS in a girl age 9 years. On August 2, DPH received a second report of HUS in a girl age 3 years from the same town. Interviews with the children’s parents revealed that the children did not know each other but that both families shopped at the same chain grocery store in town and had vacationed at the same lake in mid-July. Anecdotal reports of diarrheal illness were reported to the state and local health department from others who reported vacationing at this lake in mid-July. On August 3, the local health director was contacted. A town meeting was held August 4, and residents were warned against swimming in the lake because of suspected transmission of infection through lake water. A third case of HUS in a boy age 6 years was reported to DPH on August 5. This child lived in a different town but had spent time at the same lake in mid-July. In all 3 cases, the children stayed in housing located on the same block at the lake and reported swimming at the same beach (hereafter called beach 1).

The lake is small (approximately 190 acres) and is located in mid-southern Connecticut. The western side of the lake has approximately 380 homes. Owners are members of a lake association, and there are 3 beaches on association property. The community has 2 different water systems. By state law, all permanent residents must have their own well. Water for seasonal residents is supplied by a regional water company.

**METHODS**

**Epidemiologic Investigation**

A case was defined as diarrhea (≥3 loose stools/d for ≥3 days) in a person who was at the lake during July 16–25, 1999, in the defined geographic area. This time and area were chosen on the basis of interviews with the parents of the 3 HUS case-patients. People with chronic diarrhea were excluded as case-patients. An HUS case-patient was defined as a person who developed acute illness characterized by evidence of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment.

To determine the magnitude and source of the outbreak, we conducted a cohort study. The study population included all people who stayed at or visited homes in a defined geographic area at the lake during July 16–25, 1999. Addresses were obtained for both the seasonal and permanent residences from the town assessor records. Telephone numbers were obtained for recorded residences through telephone books, directory assistance, and neighbors. To obtain unlisted telephone numbers, we sent a newsletter to all association members. The local real estate agency was contacted, and addresses were obtained for people who had rented property at the lake during the specified time.

DPH staff contacted households by telephone from August 17 through September 10. DPH staff attempted to contact households ≥5 times, including once at night and once on weekends. Adults were interviewed by proxy for all children who were younger than 5 years. Demographic data, specific gastrointestinal symptoms, food exposures, restaurant and shopping exposures, drinking water source, participation in lake association-sponsored activities, and lake water exposures were collected using a standard questionnaire.

Statistical analyses were computed using Epi Info version 6 (CDC, Atlanta, GA). Contingency tables and Mantel-Haenszel stratified analyses were used to determine associations between various exposure activities, food and water consumption, and illness. Relative risks (RR) were calculated, and *p* ≤ 0.05 was considered significant.

**Laboratory Investigation**

We requested a stool sample from any lake resident with diarrheal illness. Stool specimens from people who met the case definition were actively sought and sent to the DPH State Laboratory for testing. Stools were cultured for *Salmonella*, *Shigella*, and *Campylobacter* using standard methods and for *E coli* O157 on sorbitol-MacConkey agar (SMAC).11,12 Broth cultures of stools were tested for Shiga toxin using the Premier enterohemorrhagic *E coli* (EHEC) enzyme-linked immunosorbent assay (ELISA), which detects Shiga toxin 1 and Shiga toxin 2. This test uses monoclonal anti-Shiga toxin capture antibody absorbed to microtiter wells.13,14 All Shiga toxin–producing isolates were sent to CDC for further testing and serotyping. Case-patients were asked to submit a serum specimen for antibody testing to lipopolysaccharides (LPS) of known STEC. ELISAs for antibodies to *E coli* O121 LPS were developed as described previously for *E coli* O157 LPS, with positive cutoff values similarly determined.15 An immunoglobulin M (IgM) titer or immunoglobulin G (IgG) titer of ≥1:320 was considered positive.

Environmental samples from sediment, drinking water, lake water, and ice were obtained and cultured for *E coli*. Each 25-g (mL) sample was suspended in 225 mL of modified *E coli* broth containing vancomycin (20 μg/mL) and incubated overnight at 37°C with aeration.16,17 Approximately 1 mL of the overnight growth was filtered through a 1000-μL micropipette tip containing a small piece of paper to remove particulate debris. Then 0.1 mL of the filtrate was plated directly onto SMAC containing cefixime (50 ng/mL) and potassium tellurite (2.5 μg/mL; SMAC-CT). A modified immunomagnetic separation procedure using anti-O157 immunomagnetic beads (Dynal, Lake Success, NY) was conducted on 1.0 mL of filtrate according to the manufacturer’s recommendations and plated onto SMAC and SMAC-CT.18 After overnight incubation at 37°C, presumptive *E coli* colonies were isolated. The original sample (0.1 mL) also was plated directly onto Levin esoin methylene blue agar and incubated overnight at 37°C, and poten-
tial E coli colonies were isolated. All isolated colonies were identified as E coli by API20E analysis (BioMerieux Vitek, Inc, Hazelwood, MO), screened for the O157 antigen using a latex agglutination test (Remel, Inc, Lenexa, KS), and tested for O157 pathogenicity gene markers using multiplex polymerase chain reaction.19 E coli isolates also were tested for Shiga toxin using standard methods.20,21

Environmental Investigation

DPH staff tested the wells and distribution points of the municipal water company and the lake water. Previous results were obtained from routine lake water testing conducted in mid-July by the lake association. Samples were tested for total coliforms and enterococcus and fecal streptococcus. DPH and local health department staff conducted an environmental evaluation of the lake on August 9–10, 1999, to identify any septic, water supply system, or other environmental conditions that could be related to the HUS/diarrheal outbreak. The entire shoreline of the lake was examined, but the main focus was on the west side, where the 3 HUS case-patients resided. All properties within 2 house lots of the lakefront were examined. An additional street was inspected because all 2 HUS case-patients stayed at houses on this block. Investigators from the Connecticut Agricultural Experiment Station surveyed the lake area and collected lake, well-water, and sediment samples on the west side of the lake on 3 different occasions during August through October 1999.

RESULTS

Epidemiologic Results

The 3 HUS case-patients were reported to the state as part of the HUS surveillance system. Twenty-five people who were not part of the cohort but who resided at the lake reported nonbloody diarrheal illnesses to the state or local health department. Stool samples were obtained from 11 of these residents.

The study cohort consisted of 211 eligible households. Of these, 165 households (78.2%) were reached, and interviews were conducted with any person who had spent time at the house during July 16–25. Forty-six households (21.8%) were not interviewed; 26 (12.3%) had unpublished or unlisted telephone numbers, and 20 (9.5%) were not reached after ≥5 attempts (including weekends and nights). Data were obtained for 436 people, 11 (2.5%) of whom had illnesses that met the case definition, including the 3 children with HUS. Seventeen people reported mild nonbloody diarrheal illness that did not meet the case definition and were included as non-ill.

Onset dates of diarrheal illness ranged from July 16 to August 4 (Fig 1). The earliest onset occurred in a toddler who was swimming with a diarrheal illness during July 16–21. Onset dates of diarrhea among the 3 HUS case-patients were July 25 and 26.

Of the 11 people who had illnesses that met the case definition, 8 were children who were younger than 12 years and 3 were adults (Table 1). The median age was 6.5 years (range: 1–62 years). Clinical characteristics included fever (27%), bloody diarrhea (27%), and severe abdominal cramping (73%). Average duration of diarrhea was 4.9 days, with an average of 6.7 stools per day. Six case-patients sought medical care. No case-patient received antibiotics for his or her illness or during the month before the illness. Only the 3 children with HUS required hospitalization. Of these, 2 required dialysis, 3 required packed red blood cell transfusions, and 2 required platelet transfusions. Average duration of hospitalization was 12.7 days (range: 4–22 days). No case-patients died.

Illness was associated with swimming on July 17 or 18 (Table 2). Those who swam on either day were 8 times more likely to develop illness. The attack rate was highest among people who were younger than 10 years and who swam on July 17 or July 18 (12%; 7 of 58). Those who swallowed water while swimming on these days were 7 times more likely to develop illness. Those who swam at beach 1 on July 17 or 18 and swallowed water were 8 times more likely to develop illness. There also was an increase in risk for those who swam longer on these days (RR = 4.8; P = .08). People who swam at beach 1 on any day were more likely to get sick than those who swam at other beaches. No illness occurred among people who

* = HUS
☐ = Case

![Graph](http://www.pediatrics.org/cgi/content/full/108/4/e59)
swam only after July 18. Illness was not associated with any particular food item, restaurant, drinking water source, or association-sponsored activity. No one who drank only municipal water developed illness.

**Laboratory Results**

Stool samples were obtained from 20 lake residents, including 11 people with reported diarrhea outside the cohort, 6 (54%) of the case-patients, and 3 people with mild diarrhea in the cohort. Initial stool samples from case-patients were received a mean of 13.7 days after the onset of symptoms (range: 1–36 days). No bacterial pathogens were isolated from the stool of any case-patient (Table 3). Among the other lake residents, *E. coli* O121:H19 was obtained from a Shiga toxin–producing isolate from 1 toddler who swam at a beach on the eastern side of the lake. This was the only Shiga toxin–producing isolate confirmed in our study.

Serum was obtained from 7 of 11 case-patients a mean of 25.7 days (range: 7–65 days) after onset of diarrheal illness. Antibody titers were positive for *E. coli* O157 in 2 of 7 case-patients (Table 3). After the *E. coli* O121 isolate was identified from 1 toddler, sera were retested for *E. coli* O121. Six of 7 case-patients had positive antibody titers; all were at least 8 times higher to *E. coli* O121 than to *E. coli* O157. Six of 7 case-patients with the development of illness. No cases were reported among people who swam only after July 18. No food item, drinking water source, or association-sponsored activity was associated with illness.

The most likely source of contamination was a toddler in diapers with onset of severe diarrhea on July 16. The toddler spent >2 hours a day in the water during the time of illness, July 16–21. The infectious dose for *E. coli* O157 is presumed to be low, and the incubation period is 1 to 8 days. Although little is known about the pathogenicity of *E. coli* O121, we expect the infectious dose and incubation period to be similar to *E. coli* O157. People in our cohort were presumed to be exposed to contaminated lake water during July 16–18; therefore, the onset of symptoms should have occurred during July 17–26. Eighty-two percent of the cases occurred during this time. Although we cannot rule out the possibility of an environmental source of contamination, this seems less plausible given the extensive environmental survey and the failure to find any environmental isolates of STEC.

The attack rate was highest among children who were younger than 10 years. This is consistent with studies of *E. coli* O157 that show that the attack rate is higher among children. Clinical characteristics were similar to those described for outbreaks caused by *E. coli* O157, although the proportion of cases with bloody diarrhea was somewhat lower (27%).

**Environmental Results**

Water samples that were collected from wells and distribution points of the municipal water system were in compliance with the standards mandated for public drinking water, except for elevated iron and manganese levels. There were no pressure drops noted in the records kept at the municipal water company. No survey to detect possible cross connections between the municipal water system and private wells was conducted.

No *E. coli* was isolated from lake water or ice cubes made in mid-July from the municipal water. The environmental evaluation of the lake conducted on August 9–10 did not identify an environmental problem that could account for the outbreak. No cattle or other livestock grazed near the lake or run-off areas. *E. coli* indicative of fecal contamination was isolated from sediment samples and water taken from a storm drain that emptied into the beach area and from a stream bed located between 2 houses, but no Shiga toxin–producing strain was identified.

**DISCUSSION**

Our findings are most consistent with a transient local beach contamination in mid-July, probably with *E. coli* O121:H19. Swimming in the lake or swallowing water on July 17 or 18 were strongly associated with the development of illness. No cases were reported among people who swam only after July 18. No food item, drinking water source, or association-sponsored activity was associated with illness.

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importance of non-O157 STEC in causing human disease.28–30 With increased international travel and importation of beef from areas such as Argentina that have a high incidence of HUS, the role of non-O157 STEC in causing human disease should be defined further.

Without HUS surveillance, this outbreak might have gone undetected by public health officials. Post-diarrheal HUS is believed to be related to the production of Shiga toxin. In previous studies of patients with HUS, *E coli* O157 was isolated more frequently in stool samples taken from a case-patient within 6 days of onset of symptoms,31–33 yet by the time patients with HUS seek medical attention (typically 1 week after the onset of diarrhea), STEC might no longer exist in the stool.

The Connecticut outbreak might have been detected sooner if Shiga toxin screening had been conducted routinely. In our study, stool samples from 2 of the HUS case-patients were tested for *E coli* O157 within 1 day of onset of diarrhea, then again at day 4 or day 11 of illness. All stools were negative for *E coli* O157. If Shiga toxin testing had been conducted on these initial broth cultures of stools collected during the bloody diarrheal phase, then *E coli* O121 might have been identified. Laboratory testing that relies solely on the inability of an isolate to ferment sorbitol will miss non-O157 STEC. Laboratories should test for Shiga toxin in appropriate clinical scenarios, such as bloody diarrhea and HUS. This would lead to a better understanding of the role of non-O157 STEC in causing human disease.

Serologic testing can be used as an adjunct in the diagnosis of STEC infections. Patients often present with HUS when they are less likely to be shedding STEC in their stool. Bacterial LPS enters the bloodstream, and an antibody response typically is seen within 7 to 10 days after infection. Previous studies reported that IgG and IgM antibodies to *E coli* O157 are good indicators of recent infection.15,34,35 In 1992,
Caprioli et al. investigated an outbreak of HUS in Italy. They isolated E. coli O111 from the stool of a case-patient and subsequently proved that 6 of 7 HUS case-patients had antibodies to O111 LPS using an ELISA-based test. There was no cross-reactivity with O157 LPS. None of 30 control subjects in this study had antibodies to O111. Other studies suggested that antibodies to some LPS are not specific and that cross-reactivity with other non-O157 STEC exists.

In the CDC laboratory (W.F.B.), we examined the reaction of sera from culture-confirmed O157 cases and O121 LPS. Our data indicate that in most cases, the reaction with O121 LPS would be considered negative, but occasionally a serum would exhibit a titer close to the homologous antigen. It seems that there is a similar cross-reaction between sera from culture-confirmed O121 cases and O157 LPS. The reaction with O157 LPS is greatly reduced, being positive only when the titer of O121 was extremely high. Thus, it seems that there is some minimal cross-reaction between the 2 antigens, but the implicated serotype can be deduced by the ratio of the reactions. The source of these cross-reactions is not known but may result from reactions with a common core LPS or another shared antigen that is co-purified along with the LPS. The sera in this study also were examined against antigens prepared to other LPS (O111, O104, and O26), and no reactions were observed. These antigens were chosen because they are responsible for the majority of the non-O157 STEC outbreaks reported in the United States.

In our study, serum was obtained a mean of 25.7 days (range: 7–65 days) after the onset of symptoms. The finding of elevated antibody titers to E. coli O121 LPS in 6 of the 7 case-patients tested, along with the epidemiologic data, strongly supports this as the cause of illness. Titers were at least 8 times higher to E. coli O121 than to O157.

Serologic results were based on a single titer and showed only an IgG response to E. coli O121 LPS. There are several reasons that could account for the lack of IgM response. One person whose serology was negative for both E. coli O121 and O157 had her serum drawn 7 days after the onset of symptoms. This person might not have mounted an immune response to the LPS antigen yet. Three case-patients had serum obtained >21 days after the onset of symptoms (range: 21–65 days). These patients had significant IgG responses, and the timing of their serology could explain the lack of IgM response. Three people had IgG responses that were >1:2560 (range: 1:2560–1:20480). The CDC laboratory (W.F.B.) found that when the IgG response is so significant, it often can block the binding of IgM to the well of the plate. We reproduced this experimentally by mixing a serum that has both an IgG and an IgM response with a second serum that has a high IgG titer. The serum is no longer positive for IgM.

This study demonstrates the usefulness of serology as an important adjunct in the identification of causative agents in STEC outbreaks. People who work in outbreak investigations should be aware of this important tool and understand its limitations. In most cases, the serologic diagnosis is very specific and cross-reactions for most serotypes of STEC are rare. However, antibody cross-reactions should be considered when interpreting serologic test results, particularly with sporadic cases of HUS. During outbreaks, determining serologic results in control subjects might help better address issues of cross-reactivity.

As demonstrated by this outbreak, non-O157 STEC are important causes of bloody diarrhea and HUS. Most non-O157 STEC would be overlooked by current laboratory practices. Without routine screening of appropriate stool specimens for Shiga toxin, valuable clinical and epidemiologic information would be missed.

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