Articles

A Cluster of *Escherichia coli* O157:H7 Infections With the Hemolytic-Uremic Syndrome and Death in California

A Mandate for Improved Surveillance

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In mid-January 1993, an outbreak of *Escherichia coli* O157:H7 infections associated with eating hamburger patties at a fast-food restaurant chain (chain A) was reported in Washington State. From mid-December to mid-January, 9 cases of *E coli* O157:H7–associated bloody diarrhea and the hemolytic-uremic syndrome had been reported in San Diego County, California. A total of 34 persons had bloody diarrhea, the hemolytic-uremic syndrome, or *E coli* O157:H7 organisms isolated from stool during the period November 15, 1992, through January 31, 1993. Organisms of *E coli* O157:H7 identified from 6 persons were indistinguishable from those of the Washington outbreak strain. Illness was associated with eating at chain A restaurants in San Diego (odds ratio, 13; 95% confidence interval, 1.7, 99) and with eating regular-sized hamburgers (odds ratio, undefined; lower-limit 95% confidence interval, 1.3). Improved surveillance by mandating laboratory- and physician-based reporting of cases of *E coli* O157:H7 infection and the hemolytic-uremic syndrome might have alerted health officials to this outbreak sooner, which could have resulted in earlier investigation and the institution of measures to prevent more cases.

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Escherichia coli O157:H7 was first identified as a pathogen in 1982 during an investigation of two outbreaks of bloody diarrhea in Michigan and Oregon.[1] It is now recognized as an important cause of the hemolytic-uremic syndrome and acute renal failure.[2] In prospective studies, *E coli* O157:H7 was identified from more than 85% of children with the hemolytic-uremic syndrome whose stool specimens were collected soon after the onset of diarrhea.[3,4] A population-based study from Washington State showed an increasing incidence of the hemolytic-uremic syndrome from the 1970s to 1980s, suggesting that the incidence of disease due to *E coli* O157:H7 may be increasing.[5]

From mid-November 1992 through mid-January 1993, the San Diego County Department of Health Services learned of nine persons with bloody diarrhea or the hemolytic-uremic syndrome; *E coli* O157:H7 was identified in stool specimens of six. Initial interviews found that four of them had eaten at one restaurant chain (chain A), but an equal number reported eating at another restaurant chain (chain B). It was initially unclear whether this was an outbreak of *E coli* O157:H7–associated illness because most cases lacked a common food source, and because there was no surveillance system for *E coli* O157:H7 or the hemolytic-uremic syndrome, background rates of illness were unknown. An intensive investigation was begun only after an outbreak associated with chain A was recognized in Washington State in mid-January[6-8] and it was determined that meat from the implicated lots may have also been distributed in southern California. The chain A–associated outbreak in Washington State was subsequently found to be linked to specific lots of ground meat produced on November 19, 1992.[8]

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Informed consent was obtained from parents or guardians of all participants.

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
CI = confidence interval
OR = odds ratio

Patients and Methods

Epidemiologic Investigation

We defined a case of *E coli* O157:H7 infection as illness in a resident of San Diego County during the period November 15, 1992, through January 31, 1993, with one or more of the following: bloody diarrhea with three or more loose stools in a 24-hour period, the hemolytic-uremic syndrome with a prodrome of diarrhea, or a stool culture that grew *E coli* O157:H7. We defined a secondary case as illness meeting the case definition in any person who reported that a household member had diarrhea in the week before his or her onset of illness.

Case Finding

Cases were identified through self-reporting, physician referral, or laboratory notification of an *E coli* O157:H7 organism. We reviewed emergency department records at five local hospitals in the northern, central, and southern parts of the county to identify cases during December 1992 and January 1993. We reviewed inpatient and clinic records at the main pediatric hospital in the county that served as a referral center for all cases of the hemolytic-uremic syndrome.

Laboratory Investigation

All case-patients who had not had stool specimens screened for *E coli* O157:H7 were asked to provide stool specimens, which were plated on sorbitol-MacConkey agar.[9] Sorbitol-negative colonies were selected and screened with O157 antisera by tube agglutination. Isolates confirmed as *E coli* through biochemical identification were then screened for immobilization with antisera to the H7 antigen. Organisms were tested for the production of Shiga-like toxins I and II using Vero cell-culture cytotoxicity[10] at the California State Department of Health Services Microbial Diseases Laboratory. Cytotoxic activity was neutralized using monoclonal antibodies against Shiga-like toxin I[11] and polyclonal and monoclonal antibodies against Shiga-like toxin II.[12] Pulsed-field gel electrophoresis was performed at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia.[13] All case-patients were also asked to provide blood specimens, which were assayed at the CDC for antibody titers to *E coli* O157 lipopolysaccharide by enzyme-linked immunosorbent assay.[14] A positive titer was defined as 1:160 or higher.

First Case-Control Study

To identify risk factors for illness, we conducted a matched case-control study using the first 25 primary case-patients identified. Controls were matched by sex, age (age groups 1 to 4 years, 5 to 9 years, 10 to 19 years, 20 to 29 years, and 30 years and more), and residential location (by adding successive single digits to the case-patient's telephone number). Only persons who denied having diarrhea (3 or more loose stools in a 24-hour period) during the outbreak period were enrolled as controls. Patients and controls were interviewed by telephone with the use of a standard questionnaire.

Second Case-Control Study

To identify food items associated with illness, we used a standard questionnaire to compare foods eaten by case-patients at chain A with those eaten by controls (meal companions) who remained well. Case-patients were matched with their own meal companions; those without meal companions were excluded.

Third Case-Control Study

To identify a possible common source for patients who did not eat at chain A, we conducted a third case-control study including only those patients who were certain they had not recently eaten at chain A. Secondary cases were excluded. Matched controls were selected as in the first case-control study.

Investigation of Restaurants and Microbiologic Testing of Hamburgers

We inspected two franchise and two company-owned chain A restaurants where case-patients had eaten. Food preparation practices were reviewed, particularly the procedures for preparing, cooking, and serving hamburgers. Information about grill types and models used by the 81 chain A restaurants in San Diego County were provided by the Operational Services Department of the parent company.

Specimens from lots of hamburger produced on November 19, 1992, and recalled from southern California and Nevada chain A restaurants were tested at the California Department of Health Services, the United States Department of Agriculture, and the University of Georgia. The following methods were used by the California Department of Health Services. Specimens of hamburger meat were incubated in modified trypticase soy broth and homogenized before passage through sterile hydrophobic grid membrane filters, which were then cultured on sorbitol-MacConkey agar and hemorrhagic-colitis medium plates.[15]

The χ^2 test used to determine matched odds ratios (OR) and exact 95% confidence intervals (CI) was calculated with Epi-Info version 5.0 and the method of Martin and Austin.[16]

Results

Descriptive Epidemiology

In all, 34 persons had illnesses that met the case definition, 10 of whom (29%) were identified through a review of emergency department records, 9 (26%) by reports from physicians, 8 (23%) through self-referral, 6 (18%) from laboratory isolates, and 1 by referral of a friend. Most illnesses began during the period mid-

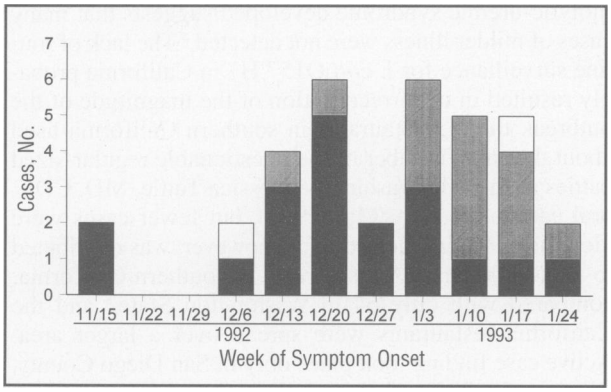

Figure 1.—The graph shows the week of onset of *Escherichia coli* O157:H7–associated illness for 34 cases in San Diego County, California, between November 15, 1992, and January 31, 1993. The black bars indicate case-patients who reported eating at chain A, the shaded bars indicate case-patients who did not report eating at chain A, and the white bars indicate case-patients who did not know if they had eaten at chain A or had secondary transmission.

December through mid-January (Figure 1), although the peak onset of illness was earlier for those patients who reported eating at chain A.

Patients' ages ranged from 1 to 58 years (median, 10 years); 20 (59%) were female. Diarrhea lasted a median of five days (range, 2 to 45 days); 33 patients (97%) described their diarrhea as bloody. Of the 34 persons, 14 (41%) were admitted to a hospital, 7 of whom had the hemolytic-uremic syndrome; one child with the syndrome died with multisystem organ failure. One patient who reported nonbloody diarrhea in a sibling in the week before onset was classified as a secondary case.

Laboratory Investigation

Stool specimens from 31 of the 34 patients were cultured. Of these, 23 were examined for *E coli* O157:H7, and 8 were positive. Of the 15 negative specimens, 13 (87%) were collected either after antibiotic use or more than ten days after the illness began. Of these 15 patients, 12 with cultures negative for *E coli* O157:H7 had cultures negative for *Salmonella, Shigella,* and *Campylobacter* species within three days after the onset of their illnesses. *Clostridium difficile* toxin was reported in the stool of 1 of these 15 patients, but a culture for *C difficile* was negative; this patient had not received antibiotics, and later the hemolytic-uremic syndrome developed. Eleven patients did not have stool specimens examined for *E coli* O157:H7. Stool cultures from eight of these were negative for *Salmonella, Shigella,* and *Campylobacter* species, and the other three had no stool testing. All eight *E coli* O157:H7 isolates produced Shiga-like toxins I and II. Pulsed-field gel electrophoresis revealed an identical electrophoretic pattern in six isolates, the same as that of the Washington outbreak strain. The two other identified organisms had patterns that differed from those of the outbreak strain and each other. Four of the six case-patients with the outbreak strain reported eating at chain A, and another was the secondary case-patient who had not eaten at chain A but whose sibling had eaten there and in whom nonbloody diarrhea developed in the week before the case-patient's illness began. The parents of the sixth case-patient said that their child had not eaten at chain A. One of the patients whose strain differed from the outbreak strain had not eaten at chain A, and the other did not remember.

Serum specimens from 9 of the 29 case-patients tested (31%) had positive antibody titers to *E coli* O157 lipopolysaccharide. Four were from persons with positive stool cultures, and two others were from children with the hemolytic-uremic syndrome. Five patients with the outbreak strain of *E coli* O157:H7 each submitted one serum specimen. Three of these, collected 30, 37, and 50 days after the onset of illness, were positive; two that were collected 4 and 23 days after the onset of the illness were negative. Of the two patients with positive stool cultures for the non–outbreak strains of *E coli* O157, one had a positive antibody titer from a specimen collected 13 days after the illness began, and one had a negative titer from a specimen collected 62 days after the illness began.

First Case-Control Study

Of the 25 primary case-patients, 15 (60%) reported eating at chain A in the ten days before the illness started, compared with 1 (4%) of 25 controls (OR, 13; CI, 1.7, 99; $P = .003$). After the two cases who did not have the outbreak strain of *E coli* O157:H7 and their matched controls were excluded, cases were still significantly more likely to have eaten at restaurant chain A than were controls (OR, 6.0; CI, 1.3, 38.8; $P = .02$). The second most frequently visited fast-food restaurant (chain B) was not significantly associated with illness. Overall, 19 (58%) of the 33 primary cases had eaten at chain A.

Second Case-Control Study

The food selected by the 12 case-patients who ate at chain A was compared with that of 19 well meal companions. Of the 12 case-patients, 10 (83%) ate regular-sized hamburgers compared with 8 (42%) of 19 meal companions (OR undefined; lower limit of 95% CI, 1.3; $P = .008$). No other food item was associated with illness.

Third Case-Control Study

Overall, 17 (89%) of the 19 case-patients who ate at chain A ate a regular-sized hamburger. These were compared with the 15 who did not eat at chain A. The median age was 7 years for the former group and 15 years for the latter ($P = .55$). As seen in Figure 1, the peak of the onset of illnesses was the week of December 20 for the former and the week of January 10 for the latter. These findings suggested that the source or mode of transmission may have differed. We therefore looked for another common source by doing a third matched case-control study that included only patients who did not report eating at chain A. Two patients were excluded: one who was a secondary case, and one who did not remember if he had eaten at chain A. Matched case-control analysis of reported exposures did not show any significant associations (Table 1).

TABLE 1.—*Third Case-Control Study: Exposures Among Case-Patients Who Did Not Eat at Chain A and Their Matched Controls*

Exposure	Cases n = 13, No. (%)	Controls n = 13, No. (%)	Matched Odds Ratio	95% CI
Any restaurant	12 (92)	8 (62)	5.0	0.7-34.0
Hamburger	9 (69)	8 (62)	2.0	0.4-11.0
Restaurant chain B	4 (31)	5 (38)	0.7	0.2-3.3
Meat purchased in store X	8 (62)	9 (69)	0.7	0.1-3.9
Day care	2 (15)	3 (23)	0.5	0.1-5.3
Chicken	9 (69)	11 (85)	0.3	0.1-2.9
Other beef	4 (31)	9 (69)	0.0	0.0-1.2
Turkey	5 (38)	4 (31)	0.0	0.0-0.2

CI = confidence interval

A higher proportion of cases than controls reported having eaten at any restaurant and having eaten hamburger in the ten days before the illness began, but the 95% confidence intervals included one.

Investigation of Restaurants and Microbiologic Testing of Hamburgers

The parent company distributed boxes of frozen patties of raw ground beef from its central distribution center to the 81 chain A restaurants in San Diego County. Of these 81 restaurants, 16 were named by patients. Of these 16 restaurants, 4 (25%) were franchises, and the others were company owned; similarly, 25% of chain A restaurants in the county were franchises. The grill type used in 10 (62%) restaurants named by patients was the same as that used in 53 (65%) chain A restaurants in the county.

Cooking procedures were similar at the two franchise and two company-owned restaurants visited. At both restaurants, regular-sized frozen hamburger patties, which were not prethawed, were cooked during the outbreak for one minute per side.

Investigations in Washington State linked illness to regular-sized hamburger patties produced on November 19, 1992.[6-8] *Escherichia coli* O157:H7 cultured from regular-sized hamburger patties recalled from southern California and Nevada had an electrophoretic pattern that was identical to that of organisms from six patients in San Diego and to those of the Washington outbreak strain. The suspect regular-sized hamburgers had been distributed to chain A restaurants in southern California from December 7 through December 21, 1992 (Jessica Tuttle, MD, Foodborne and Diarrheal Diseases Branch, CDC, Atlanta, Georgia, oral communication, May 1993). A total of 697 boxes containing 278,800 suspect regular-sized patties were distributed in southern California and Nevada; only 42 of these boxes were returned after the company's recall order, which was issued on January 18, 1993; presumably the patties in the other boxes had been eaten (Jessica Tuttle, MD, CDC, oral communication, May 1993).

Discussion

The large proportion of patients in San Diego County who were admitted to a hospital or in whom the hemolytic-uremic syndrome developed suggests that many cases of milder illness were not detected.[2] The lack of routine surveillance for *E coli* O157:H7 in California probably resulted in underrecognition of the magnitude of the outbreak there. Restaurants in southern California used about the same number of the questionable regular-sized patties as those in Washington (Jessica Tuttle, MD, CDC, oral communication, May 1993), but fewer cases were identified. The implicated meat, however, was distributed to about 400 chain A restaurants in southern California, compared with only 64 in Washington State,[8] and the California restaurants were spread over a larger area. Active case finding took place only in San Diego County, where only 20% of the southern California chain A restaurants that received the implicated meat are located. Although California newspapers reported the outbreak, health departments in California did not issue statements recommending that persons with bloody diarrhea visit their physicians so that stool specimens could be appropriately cultured, as was done in Washington. Moreover, few laboratories in California routinely culture stools for this pathogen, and the reporting of *E coli* O157:H7 infection was not required. For example, only two of nine major hospital laboratories surveyed in January 1993 in San Diego County routinely cultured even bloody stools for this organism. In contrast, bloody stools are more frequently cultured for this pathogen in Washington State (Beth Bell, MD, Washington State Department of Health, Seattle, oral communication, May 1993), where mandatory reporting of *E coli* O157:H7 infection was instituted in 1987.[17]

Because the peak of cases in San Diego occurred earlier than the peak in Washington State,[7] identification and recognition of the source of the chain A–associated illnesses in San Diego might have led to measures that could have interrupted the outbreak sooner. There are several possible reasons why the outbreak was not detected sooner in San Diego: *E coli* O157:H7 was not reportable in California, the rate of background infection was not known, and hospitals were not routinely culturing for the organism. Furthermore, interviews of the nine case-patients who were initially reported to the county health department in December did not reveal a restaurant source that was common to most of the cases: four persons had eaten at one restaurant chain, and four had eaten at a different restaurant chain.

We were unable to identify other food sources of infection for persons with illness who did not eat at restaurant chain A. At least some of these cases most likely represent sporadic background cases that occur year-round but could not be documented as such because of the lack of a surveillance system. Although a higher proportion of case-patients than control persons ate at restaurants and ate hamburgers, these trends were not statistically significant. This finding may be attributable partly to small sample size, but several sources of infection are likely. Two patients had *E coli* O157:H7 strains that differed from one another and from the outbreak strain; other patients may also have had another source of

infection or had illness due to another pathogen. The observation, however, that one patient who denied eating at chain A had the outbreak strain suggests that other patients with no known connection to chain A could have been part of the outbreak as well. Some cases may have been misclassified; for example, parents who provided food histories for their ill children may not have known that their children had eaten at a chain A restaurant. Or more cases may have been due to secondary spread than the one recognized. In addition, some of the questionable meat, besides being supplied as patties to restaurant chain A, was distributed as ground beef to other restaurants and to grocery stores in southern California (Jessica Tuttle, MD, CDC, oral communication, May 1993).

The outbreak of *E coli* O157:H7 infections in San Diego County was part of the largest *E coli* O157:H7 outbreak yet recorded, involving four states and causing laboratory-confirmed illness in more than 500 people.[7,8] The magnitude of this outbreak emphasizes the potential for a multistate outbreak when a contaminated product is widely distributed. Improved surveillance for *E coli* O157:H7 and the hemolytic-uremic syndrome is needed so that outbreaks can be recognized and control measures quickly implemented. We recommend that laboratories routinely culture diarrheal stool specimens for *E coli* O157:H7 using sorbitol-MacConkey medium; at a minimum, this pathogen should be sought in the stools of all persons with bloody diarrhea. The serologic test for antibodies to O157 lipopolysaccharide is still experimental, and its sensitivity and specificity vary when used in different settings.[14] Of all patients identified as cases, 31% in our study had elevated antibody titers, compared with 53% of patients in the previous study.[14] The serologic test is done only in reference laboratories and will remain a research tool until the pattern of the serologic response to infection with *E coli* O157:H7 is better characterized.

More outbreaks of *E coli* O157:H7 have been linked to undercooked ground beef than to any other vehicle.[2] Several possible approaches may reduce the risk of illness due to this pathogen in meat products. In response to this outbreak, on January 28, 1993, the Food and Drug Administration issued interim recommendations for the cooking of all ground beef products to at least 68°C (155°F), rather than the previously recommended internal temperature of 60°C (140°F).[18] In addition, the Food Safety and Inspection Service of the United States Department of Agriculture now requires that safe food-handling labels be placed on all packages of raw meat products at the point of retail sale.[19]

Surveillance in California for this pathogen will be improved. Regulations have been proposed to make this infection reportable by both laboratories and health care professionals and to make the hemolytic-uremic syndrome reportable by health care professionals. To improve the timely detection of future outbreaks, though, physicians and laboratory personnel must be educated in the appropriate indications for and methods of testing for this organism. In addition, people who work in the food industry must be educated to cook hamburgers according to current recommendations, and consumers must demand that hamburgers served at home or in restaurants be cooked until no trace of pink color remains.

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