Hemorrhagic Colitis Associated with a Rare Escherichia coli Serotype


The paper by Riley et al., from the Centers for Disease Control and state and local health departments in Oregon and Michigan, described for the first time what was later called EHEC (enterohemorrhagic Escherichia coli) diarrhea. The authors could exclude all known infectious diarrheagenic agents except E. coli serotype O157:H7 as the possible cause of this infection. It was characterized by abdominal cramps, initially watery and later bloody diarrhea, occasional fever, and blood (but not intestinal) leukocytosis. The symptoms lasted from 3 to >7 days and were not influenced by antimicrobial agents. The same serotype was detected in beef patties consumed by the patients but not in healthy individuals or in patients with diarrhea caused by other agents. Infant rabbits infected with E. coli O157:H7 exhibited diarrhea, albeit nonbloody diarrhea.

In the years after the report, the unique character of this gastrointestinal disorder became clear. By now, ca. 160 serovars of E. coli are known to produce so-called verotoxins (VT1 and VT2), which produce hemorrhagic lesions in the distal ileum and colon. Their detection is best done today by PCR or colony hybridization methods. The source is the gastrointestinal tract of cattle, of other farm animals, and occasionally of humans. The clinical and epidemiological importance of EHEC has become clear in the past decade. Undercooked beef and raw milk are the main sources of human infections, and 5 to 10% of the latter may give rise to serious complications in children, i.e., hemolytic uremic syndrome and thrombotic thrombocytopenic purpura.

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HEMORRHAGIC COLITIS ASSOCIATED WITH A RARE ESCHERICHIA COLI SEROTYPE


Abstract We investigated two outbreaks of an unusual gastrointestinal illness that affected at least 47 people in Oregon and Michigan in February through March and May through June 1982. The illness was characterized by severe crampy abdominal pain, initially watery diarrhea followed by grossly bloody diarrhea, and little or no fever. It was associated with eating at restaurants belonging to the same fast-food restaurant chain in Oregon \( (P < 0.005) \) and Michigan \( (P = 0.0005) \) and with eating any of three sandwiches containing three ingredients in common (beef patty, rehydrated onions, and pickles).

In the first half of 1982 two outbreaks of an unusual gastrointestinal illness characterized by sudden onset of severe abdominal cramps and grossly bloody diarrhea, with no fever or low-grade fever, occurred in Oregon and Michigan. Isolated cases of a similar illness had recently been reported from Japan and the United States, but the etiologic agent had not been identified. The outbreaks in Oregon and Michigan led to intensive epidemiologic and laboratory investigations. In this report we describe the illness and the evidence that it is associated with a rare serotype of Escherichia coli that is neither invasive nor enterotoxigenic according to standard tests and is not a recognized enteropathogenic E. coli.

METHODS

Epidemiologic Investigation

We defined as a case an illness characterized by severe abdominal cramps, grossly bloody diarrhea, and stool examinations that did not yield Shigella, salmonella, campylobacter, ova, or parasites.

To find cases, we contacted local physicians, reviewed records of chief complaints in emergency rooms and discharge records from December 1981 to February 1982 in parts of Oregon, and from May to June 1982 in parts of Michigan, and began active surveillance in all hospitals in the affected areas and nearby counties. In both states
we conducted case-control studies with either one or two age-matched and neighborhood-matched controls for each case, using a questionnaire developed after intensive interviews of reported cases. We examined specific food exposures at restaurants implicated by the Michigan neighborhood case-control study, by comparing foods eaten by cases and by controls selected from persons who had visited the restaurants with the cases and had remained well. Food-handling procedures, food delivery and turnover, and employee records were reviewed at the implicated restaurants. In Michigan, grill temperature was measured in one implicated restaurant by means of a rapid readout surface pyrometer (Pyronix, type 4000A, Alnor Instruments). Logistic regression analysis, the binomial test, and the Pike–Morrow extension of the Mantel–Haenszel test were used for statistical analyses.6

Laboratory Investigation
Stool specimens from cases were examined at the local hospital and state health-department laboratories for salmonella, shigella, campylobacter, ova, and parasites in both states and for Yersinia enterocolitica in Oregon. Stool specimens from some cases and controls were frozen (−70°C) until examination at the Centers for Disease Control (CDC). In Oregon, stool specimens were also collected from 45 persons who visited emergency rooms because of nonbloody diarrhea. Environmental samples, including food, were collected at implicated food establishments.

At the CDC, stool specimens from the outbreaks were examined for salmonella, shigella, pathogenic vibrios, Y. enterocolitica, campylobacter species, bacillus species, Staphylococcus aureus, enterotoxogenic and enteroaggregative E. coli, and anaerobes (including Clostridium difficile and toxin). Five E. coli isolates from each stool were serotyped. The stool specimens were also examined for viruses by electron microscopy, by immunoelectron microscopy with acute-phase and convalescent-phase serum, and by culture in rhesus-monkey and human-fibroblast tissue cells.8,9 The 45 diarrheal stool specimens obtained at emergency rooms were examined for E. coli 0157 and klebsiella. The foods were examined for E. coli 0157 and Bacillus pumilus.

E. coli 0157:H7, Klebsiella oxytoca, and B. pumilus isolates were tested for invasiveness by the Sereny test, for heat-stable toxin production by the sucking-mouse assay, and for heat-labile toxin production by the Y-1 adrenal-cell test.10 E. coli 0157:H7 was tested in an infant-rabbit assay (Potter ME: personal communication).

The E. coli serotyping records of the U.S. Department of Agriculture Animal Laboratories at Ames, Iowa, the Pennsylvania State University Veterinary Science Laboratory, and the CDC Enteric Reference Laboratory were reviewed for previous identifications of E. coli 0157:H7.

Case Report
The following case report is typical of the cases seen in both outbreaks. A 36-year-old man was awakened by severe abdominal cramps in the right lower quadrant. Later the same morning, watery diarrhea developed, with bowel movements every 15 to 30 minutes. The patient initially noted small amounts of blood, but later the same day the diarrhea became grossly bloody, with bright-red blood, described as "all blood and no stool." He had slight nausea but no vomiting. He was hospitalized on the following day with continuous crampy abdominal pain and frequent bloody diarrhea. He was afebrile and on abdominal examination had no guarding, rebound tenderness, or distension. The white-cell count was 17,900 with a slight shift to the left. A barium enema revealed edema of the ascending and transverse colon, with areas of spasm. Examinations of three stool specimens collected within three days after the onset of illness did not detect salmonella, shigella, campylobacter, yersinia, or parasites. The patient was treated with intravenous fluids and doxycycline, and the bloody diarrhea subsided by the fifth hospital day. He was discharged the next morning.

Results
Clinical and Epidemiologic Investigations
In Oregon, 25 persons from seven municipalities in one county and one person from an adjacent county became ill between February 5 and March 15 (Fig. 1). The median age was 28 years, with a range of 8 to 76 years; there were 16 males and 10 females. All consulted a physician, and 19 (73 per cent) were hospitalized. The duration of illness ranged from two to nine days, with a median of four days. In Michigan, 21 persons had onset of illness between May 28 and June 27 (Fig. 1). The median age was 17 years, with a range of 4 to 58 years. All consulted a physician, and 14 (67 per cent) were hospitalized. The illness lasted from three to more than seven days.

The symptoms in both outbreaks are shown in Table 1. Three patients in both outbreaks had temperatures of 38.5°C or more. The white-cell count ranged from 7600 to 19,600 (mean, 14,000) in Oregon and from 7600 to 17,400 (mean, 13,000) in Michigan, with a slight to moderate shift to the left. The erythrocyte sedimentation rates, serum electrolyte concentrations, liver-function tests, prothrombin times, and urinalyses were normal in all patients in whom these tests were done. Sigmoidoscopy performed in 10 patients revealed moderately hyperemic mucosa in 3. In six of seven patients barium enemas demonstrated marked submucosal edema with spasm and a "thumb-printing" pattern in the ascending and transverse colon (Fig. 2). In Oregon, 11 of 23 patients whose treatment histories were available received tetracycline compounds (eight patients) or erythromycin (three patients). The mean duration of illness of the group treated with antimicrobials was not significantly different from that of the untreated group. No transfusions were administered. There were no deaths, complications, or sequelae in any of the cases.

In Oregon, 25 of 26 cases and 47 neighborhood controls were interviewed. During the two weeks before onset of illness, 21 of 25 cases (84 per cent) but only 13 of 47 controls (28 per cent) had eaten at Restaurant 1,
one of a chain of fast-food restaurants (Chain A) 
(P<0.005 by logistic regression analysis). Three of the 
four who did not recall having eaten at Restaurant 1 
had eaten at another Chain A restaurant within a week 
before the onset of illness.

The patients who ate at one of the three restaurants 
of Chain A in the county were more likely (21 of 24) to 
have eaten one of the chain’s specialty hamburgers 
than were neighborhood controls (11 of 20) who had 
eaten at the same restaurants (P<0.05, logistic regres-
sion analysis). The three patients who did not eat a 
specialty hamburger ate a regular hamburger (one pa-
tient) or a cheeseburger (two patients). The three 
types of sandwiches shared three ingredients, which 
were always served together — i.e., reconstituted de-
hydrated onions, standard-size hamburger meat pat-
ties, and pickles. Each of these three ingredients was 
eaten by a higher proportion of cases than of neighbor-
hood controls (P<0.05, Pike–Morrow extension of the 
Mantel–Haenszel test), but no single ingredient could 
be independently associated with disease, because 
they had always been served together.

In Michigan, 18 of 21 cases and their age-matched 
neighborhood controls were interviewed. (Matched 
controls could not be found for two cases.) Seventeen 
of 18 cases and 4 of 16 controls had eaten at either 
Restaurant 2 or Restaurant 3 of Chain A within 10 
days before the onset of illness (P = 0.0005, binomial 
test). No other exposures were significantly associated 
with illness. Again, cases were more likely than their 
restaurant controls to have eaten the same three food 
items implicated in Oregon (17 of 17 vs. 12 of 19; 
P<0.05, Pike–Morrow extension of the Mantel– 
Haenszel test). The mean period between single expo-
sures to the implicated foods and onset of crampy ab-
dominal pain was 3.9 days in Oregon and 3.8 days in 
Michigan. The attack rate for persons eating sand-
wiches that included the three ingredients was esti-
mated to be about 1 case per 1000 sandwiches in Oregon, 
and 1.8 cases per 1000 for specialty hamburgers in 
Michigan, and 0.6 case per 1000 regular hamburgers 
and cheeseburgers in Michigan. The specialty ham-

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>OREGON (N = 25)</th>
<th>MICHIGAN (N = 18)</th>
<th>COMBINED (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloody diarrhea †</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Abdominal cramps †</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Nausea</td>
<td>60</td>
<td>67</td>
<td>63</td>
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<tr>
<td>Vomiting</td>
<td>44</td>
<td>61</td>
<td>49</td>
</tr>
<tr>
<td>Chills</td>
<td>28</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>URI symptoms ‡</td>
<td>12</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Fever (&gt;38°C)</td>
<td>8</td>
<td>6</td>
<td>7</td>
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*Based on all cases with complete clinical history.
†Part of case definition. ‡Upper-respiratory-tract infection.

The area of "thumbprinting" (arrow) in the transverse colon sug-
gests submucosal edema, a characteristic finding in this disease.

burger had twice the quantity of meat (two patties vs. 
one) and onions as the regular hamburger or cheese-
burger.

Only one case of bloody diarrhea occurred among 
employees at the three restaurants. None of the family 
members of the cases in Oregon and Michigan had 
 bloody diarrhea. In Michigan, 4 of 13 persons who had 
accompanied the cases to the implicated restaurants 
and had eaten one of the implicated foods had cramps 
and diarrhea without blood in one to seven days, 
whereas none of 12 who had not eaten these foods were 
ill (P = 0.06, Fisher's exact test, one-tailed).

There were no obvious defects in equipment or food-
handling practices in the Oregon or Michigan restaur-
ants. In Michigan, inadequate stock rotation of some 
foods was observed in Restaurant 2, and during busy 
periods certain parts of the grill were cooler than the 
temperature standard established by Chain A.

**Laboratory Investigation**

*E. coli* 0157:H7, *B. pumilus*, and *K. oxytoca* were the 
only bacteria isolated from three or more cases in ei-
ther outbreak. *E. coli* 0157:H7 was recovered from 
stoil of three of six Oregon cases and none of 10 neigh-
borhood controls (P = 0.03, Fisher's exact test, one-
An additional patient with \textit{E. coli} 0157:H7 was identified by screening \textit{E. coli} isolates sent to the CDC from Oregon. \textit{K. oxytoca} was isolated from two cases and no controls (it was isolated in Oregon from one of the controls); \textit{B. pumilus} was isolated from two cases and one control. \textit{Y. enterocolitica} was recovered from one case only on cold enrichment, suggesting small numbers of organisms. Examination of the 45 control emergency-room diarrheal stool specimens yielded \textit{K. oxytoca} from two samples and \textit{E. coli} 0157:H7 from none. In the virologic studies we did not detect viral particles on electron microscopy or immunoelectron microscopy or in tissue cultures.

\textit{E. coli} 0157:H7 was recovered from 6 of 14 specimens from cases and none of 4 specimens from controls in Michigan. \textit{K. oxytoca} and \textit{B. pumilus} were each isolated from three cases. In both states combined, \textit{E. coli} 0157:H7 was isolated from 9 of 12 stools collected within four days after the onset of illness, but from none of 7 stools collected seven or more days after onset (P = 0.002, Fisher’s exact test, one-tailed). In both outbreaks 0157:H7 was the predominant \textit{E. coli} isolated (median of four of five isolates serotyped). The serotypes of \textit{K. oxytoca} from patients’ stools were different. The \textit{E. coli} and \textit{K. oxytoca} were sensitive to all antimicrobial agents tested, and the \textit{B. pumilus} had two different antimicrobial-susceptibility patterns.

\textit{E. coli} 0157:H7 was not isolated from food samples collected in Oregon but was isolated from a frozen, raw, standard-size hamburger patty from a suspected lot used at the Michigan restaurants during the outbreak period. This patty had been stored at a processing plant in another state, as part of a quality-control program, and had never been in either restaurant.

\textit{E. coli} 0157:H7 did not produce either heat-labile or heat-stable enterotoxin, nor were isolates invasive on Sereny testing or tissue-culture assays. The organism, however, did produce a nonbloody diarrhea in infant rabbits. The laboratories of the U.S. Department of Agriculture and Pennsylvania State University reported no \textit{E. coli} 0157:H7 from animals in the United States. The CDC laboratory detected only one strain of \textit{E. coli} 0157:H7 among over 3000 \textit{E. coli} organisms serotyped since 1973; it was isolated from a 50-year-old California woman in 1975 during an acute, self-limited afibrile illness with severe abdominal cramps followed by grossly bloody diarrhea.

**DISCUSSION**

Two outbreaks of a clinically distinctive diarrheal illness occurred three months apart in two widely separated areas of the country among persons who had eaten at restaurants of a single fast-food chain. A rare \textit{E. coli} serotype, 0157:H7, was isolated from ill patients in both outbreaks and from a retained specimen of hamburger patty from a suspected lot in the Michigan outbreak. We hypothesize that on two occasions, \textit{E. coli} 0157:H7 contaminated the meat before it was made into hamburger patties, survived the cooking procedures at the restaurants, and caused illness among some people who ate the meat. Apparently, failure to use meat by lots permitted cases to occur during a prolonged period in both outbreaks. The low attack rate in both outbreaks suggested a low level of contamination of a large volume of raw meat, reduction of the inoculum by cooking, or unknown host susceptibility factors. The pathogenesis of the illness and the source of contamination of the raw meat by this \textit{E. coli} serotype are not known.

The evidence that \textit{E. coli} 0157:H7 was the etiologic agent in these outbreaks may be summarized as follows. In two outbreaks this serotype was isolated from ill persons but not from healthy persons, ill persons with other forms of diarrhea, or patients who had completely recovered from bloody diarrhea. The only other isolate of \textit{E. coli} 0157:H7 identified at the CDC was from a patient who had an identical disease in 1975. Preliminary studies indicate that this \textit{E. coli} produces nonbloody diarrhea in infant rabbits, whereas \textit{E. coli} isolates from two human control stool specimens do not (Potter ME: personal communication).

The clinical presentation of this illness may be distinguished from that of the bloody diarrhea or dysentery described in shigellosis, amebiasis, campylobacteriosis, or invasive \textit{E. coli} gastroenteritis by the lack of fever and the bloody discharge resembling lower gastrointestinal bleeding. However, like other causes of bloody diarrhea, \textit{E. coli} 0157:H7 may produce a spectrum of illness. In Michigan there was evidence of nonbloody diarrhea among persons who ate the same foods implicated at restaurants of Chain A. Our case definition, which required the presence of bloody diarrhea, would have excluded milder cases of this illness.

The case report of bloody diarrhea associated with \textit{E. coli} 0157:H7 in 1975 suggests that this disease has occurred sporadically in the past. Descriptions of sporadic cases of a similar illness, frequently associated with antimicrobial use and distinct from pseudomembranous colitis, have been reported from several countries, including Japan and the United States.\textsuperscript{11,12} Sakurai et al. reported that colonoscopy revealed areas of diffuse mucosal hemorrhage or erosion, mostly in the right colon; biopsy specimens of the mucosa showed little or no inflammatory change.\textsuperscript{1} In the Oregon and Michigan outbreaks, only one patient in Oregon had been receiving an antibiotic (penicillin) before the onset of illness. Other reports have described cases of hemorrhagic colitis not associated with antimicrobial agents\textsuperscript{1} or cases of so-called ischemic colitis in young adults.\textsuperscript{11} Some of these may represent sporadic cases of the same illness that we have described in these outbreaks.

Acute hemorrhagic enterocolitis has been reported in patients with \textit{K. oxytoca} isolated from their stools,\textsuperscript{12} but no control stool cultures were obtained. In the two outbreaks that we investigated, strains of \textit{K. oxytoca} were of several serotypes and were isolated from cases and controls. Although \textit{B. pumilus} can induce enterocolitis in guinea pigs given clindamycin,\textsuperscript{13} the \textit{B. pumilus} isolates obtained in the two outbreaks were isolated...
from both cases and controls and appeared to include more than one strain.

*E. coli* can cause diarrhea by direct invasion of the intestinal mucosa and by elaboration of heat-stable enterotoxins or of heat-labile resembling cholera toxin. Our laboratory studies have shown that strain 0157:H7 does not cause disease by these mechanisms. Strains of *E. coli* that cause diarrhea by poorly defined mechanisms have been studied, but they do not typically cause bloody diarrhea.\(^{17-19}\) *E. coli* 0157:H7 may cause diarrhea by an as yet unknown mechanism, perhaps by the production of previously unrecognized enterotoxins.

Isolation of *E. coli* 0157:H7, a rare serotype, from cases in two outbreaks of bloody diarrhea, from the suspected vehicle for the outbreaks, and from a sporadic case of bloody diarrhea in 1975 strongly suggests, but does not prove, that it caused the illness; proof may require studies using animal models and perhaps human volunteers. Similarly, the epidemiology, clinical spectrum, and pathogenesis of this unusual illness and the reservoir of the putative etiologic agent are still poorly understood or unknown and require continued clinical, epidemiologic, and laboratory studies.

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### References