Epidemic Profile of Shiga-Toxin–Producing Escherichia coli O104:H4 Outbreak in Germany — Preliminary Report

Christina Frank, Ph.D., Dirk Werber, D.V.M., Jakob P. Cramer, M.D., Mona Askar, M.D., Mirko Faber, M.D., Matthias an der Heiden, Ph.D., Helen Bernard, M.D., Angelika Fruth, Ph.D., Rita Prager, Ph.D., Anke Spode, M.D., Maria Wadl, D.V.M., Alexander Zoufaly, M.D., Sabine Jordan, M.D., Klaus Stark, M.D., Ph.D., and Gérard Krause, M.D., Ph.D., for the HUS Investigation Team*

ABSTRACT

BACKGROUND
In this report, we provide a preliminary description of an ongoing large outbreak of gastroenteritis and the hemolytic–uremic syndrome caused by Shiga-toxin–producing Escherichia coli in Germany in May and June 2011.

METHODS
We analyzed data from reports in Germany of Shiga-toxin–producing E. coli gastroenteritis and the hemolytic–uremic syndrome and clinical information on patients presenting to Hamburg University Medical Center. An outbreak case was defined as a reported case of the hemolytic–uremic syndrome or of gastroenteritis in a patient infected by Shiga-toxin–producing E. coli, serogroup O104 or serogroup unknown, with an onset of disease on or after May 1, 2011, in Germany.

RESULTS
As of June 18, 2011, a total of 3222 outbreak cases (including 39 deaths) have been reported in Germany, 810 of which (25%) involved the hemolytic–uremic syndrome. The outbreak is centered in northern Germany and peaked around May 21 to 23. Most of the patients in whom the hemolytic–uremic syndrome has developed are adults (89%; median age, 43 years), and women are overrepresented (68%). The estimated median incubation period is 8 days, with a median of 5 days from the onset of diarrhea to the development of the hemolytic–uremic syndrome. Among 59 patients infected with the outbreak strain who were prospectively followed at Hamburg University Medical Center, the hemolytic–uremic syndrome developed in 12 (20%), with no significant difference between patients in whom the syndrome developed and those in whom it did not with respect to sex or reported initial symptoms and signs. The outbreak strain was typed as an enteroaggregative Shiga-toxin–producing E. coli O104:H4, producing extended-spectrum beta-lactamase.

CONCLUSIONS
In this large outbreak of the hemolytic–uremic syndrome, caused by an unusual strain of Shiga-toxin–producing E. coli, cases have occurred predominantly in adults, with a preponderance of cases occurring in women. The hemolytic–uremic syndrome has developed in a quarter of the symptomatic outbreak cases that have been ascertained thus far.
On May 19, 2011, the Robert Koch Institute, Germany’s national-level public health authority, was informed about a cluster of three cases of the hemolytic–uremic syndrome in children admitted on the same day to the university hospital in the city of Hamburg. On May 20, a team from the Robert Koch Institute arrived in Hamburg to assist with the public health investigation. It quickly became clear that the case numbers were continuing to rise, that there were also cases in adults, and that other areas of Germany, especially northern Germany, were also affected. An investigation of the outbreak involving all levels of public-health and food-safety authorities was initiated to identify the causative agent and the vehicle of infection in order to prevent further cases of disease.

The hemolytic–uremic syndrome, which was first described in children in the 1950s, is characterized by the triad of acute renal failure, hemolytic anemia, and thrombocytopenia. Diarrhea-associated hemolytic–uremic syndrome occurs primarily in children, and a precipitating infection with Shiga-toxin–producing Escherichia coli, mainly of serotype O157:H7, is the primary cause. The usual reservoir for these bacteria is ruminants, particularly cattle. Human infection with Shiga-toxin–producing E. coli occurs through the inadvertent ingestion of fecal matter — for example, through contaminated food or water or through contact with animals or their farm environment or, secondarily, through contact with infected humans. In contrast, the hemolytic–uremic syndrome with prodromal diarrhea, indicating an infectious cause, is a rare event in adults. For example, from 1989 through 2006, only 21 of the 322 adults (7%) listed in the Oklahoma registry as having thrombotic thrombocytopenic purpura or the hemolytic–uremic syndrome presented with bloody diarrhea.

This report provides descriptive epidemiologic, clinical, and microbiologic information on this unusual outbreak. It will be updated after the outbreak has finally ceased, in order to provide a complete picture.

**Methods**

**German Surveillance System**

According to the German Protection against Infection Act of 2001, the detection of a Shiga toxin (Stx) in E. coli isolates or of its encoding gene (stx) in stool enrichment culture or isolates must, by law, be reported by diagnosing laboratories to local health departments. This reporting process allows the identification of Shiga-toxin–producing E. coli infection independently of serogroup (serotyping information is requested but not required). The German case definition of Shiga-toxin–producing E. coli gastroenteritis (without the hemolytic–uremic syndrome) requires, besides laboratory confirmation, the presence of at least one of the following symptoms: diarrhea (three or more loose stools in a 24-hour period), abdominal cramps, or vomiting.

In addition, physicians are required to report clinical symptoms compatible with diarrhea-associated hemolytic–uremic syndrome in a patient. The German case definition of the hemolytic–uremic syndrome comprises thrombocytopenia (platelet count of <150,000 per cubic millimeter), hemolytic anemia, and acute renal dysfunction. The third criterion is met if at least one of the following findings is present: an increase in the serum creatinine level (unspecified), oliguria, anuria, proteinuria, or hematuria.

Reported cases of the hemolytic–uremic syndrome or Shiga-toxin–producing E. coli infection are investigated and recorded by the local health department, and the reports are forwarded electronically, without identifying information, through the state to the federal level. To minimize the delay that might result from the local investigation of the details of a case, the Robert Koch Institute, on May 23, asked all health departments to immediately forward all case reports of suspected or confirmed hemolytic–uremic syndrome, relying on the diagnoses of the notifying clinicians. Case details such as clinical and microbiologic information are to be added to the record by local health departments in the future.

Disease onset was defined as the onset of diarrhea, regardless of whether the hemolytic–uremic syndrome developed at a later date. An outbreak case was defined as a reported case of the hemolytic–uremic syndrome or a reported case of gastroenteritis in a patient infected by Shiga-toxin–producing E. coli, of serogroup O104 or unknown serogroup, with a disease onset on or after May 1, 2011, in Germany. We describe here data from the national reporting database on in-
fectedious diseases as of June 18, 2011, at 6 p.m. Central European Summer Time. The preliminary descriptive analysis focuses primarily on reported cases of the hemolytic–uremic syndrome in Germany as an indication of the entire outbreak. To show the outbreak area, a map of the incidence of the disease according to county is provided (Fig. 2). Since many cases even within Germany are apparently travel-related, a map showing the incidence according to the patients’ residence would be misleading. Therefore, for each presumed county of infection, we counted in the numerator both cases among residents of the county who did not have a history of travel and those among case patients who resided elsewhere and had a history of travel to that county; the denominator was the residential population of the county.

**CLINICAL INFORMATION**

We analyzed clinical data from two groups of patients at the Hamburg University Medical Center (HUMC): patients at their first presentation to the HUMC between May 19 and June 1 who were positive for stx (data extracted from electronic medical records) and a cohort of adults who were seen between May 25 and June 6 at a Shiga-toxin–producing E. coli unit that was set up during the course of this outbreak. The study protocol was approved by the ethics committee of the Hamburg Chamber of Physicians. Patients were enrolled in the study if they presented with bloody diarrhea or if they had any diarrhea after contact with a patient who had Shiga-toxin–producing E. coli infection. All patients provided written informed consent before enrollment. Patients were followed for at least 14 days and were tested for the outbreak strain according to the protocol of the National Consulting Laboratory on Hemolytic–Uremic Syndrome. Only data from patients infected by the outbreak strain were included in the analysis. The proportion of patients with the hemolytic–uremic syndrome among all patients who were positive for Shiga-toxin–producing E. coli was calculated. Platelet counts and creatinine and lactate dehydrogenase levels were monitored daily.

**MICROBIOLOGIC ANALYSIS**

Shiga-toxin–producing E. coli infection is diagnosed by private microbiologic laboratories either by screening for Stx with the use of one of several commercially available enzyme immunoassays or by detection of stx with the use of polymerase chain reaction (PCR). The National Reference Centre for Salmonella and Other Bacterial Enteric Pathogens confirms, culturally isolates, and characterizes Shiga-toxin–producing E. coli from samples in local or regional laboratories that are positive for Stx or stx. Chromogenic agar media for Enterobacteriaceae that are positive for extended-spectrum beta-lactamase (ESBL) are used for isolation of the strain. Biochemical characterization of the strain was performed with the use of various commercially available tests (VITEK, bioMérieux; MicroPlate GN, BIOLOG; and API, bioMérieux). Shiga-toxin–producing E. coli virulence-factor genes (stx₁, stx₂, eae, and ehx) are detected by established PCR methods. The presence of virulence-factor genes that are typical of enteroaggregative E. coli, such as aatA, aggR, aap, aggA, and aggC, are detected according to established PCR protocols. Antimicrobial susceptibility was tested by means of microdilution assays with the use of minimal inhibitory concentrations according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing. Serotyping of Shiga-toxin–producing E. coli followed standard protocols. One-enzyme (Xba1) pulsed-field gel electrophoresis was performed on Shiga-toxin–producing E. coli O104:H4 isolates. Given the strain’s properties, a shortened protocol is recommended by the National Consulting Laboratory on Hemolytic–Uremic Syndrome and is currently used by the National Reference Centre and HUMC for confirmation of the outbreak strain.

**STATISTICAL ANALYSIS**

For statistical comparisons, the z test was used for proportions, and the Mann–Whitney U test for age distribution. The incubation period was estimated on the basis of data from selected patients with the hemolytic–uremic syndrome or Shiga-toxin–producing E. coli gastroenteritis for whom the date of onset of diarrhea was known and who had stayed in northern Germany for no more than 48 hours. The interval between the date of onset of diarrhea and the date of diagnosis of the hemolytic–uremic syndrome was calculated with the use of information from the clinician’s notification form, which was sent...
without identifying information to the Robert Koch Institute.

RESULTS

OUTBREAK CASES

As of June 18, 2011, a total of 810 cases of the hemolytic–uremic syndrome, including 27 fatal cases (3.3%), and 24,12 additional cases of Shiga-toxin–producing E. coli gastroenteritis (all laboratory-confirmed), including 12 fatal cases (0.5%), were reported in Germany, with onset dates of May 1 or later. Thus, the hemolytic–uremic syndrome developed in 25.1% of the patients ascertained in this outbreak. The outbreak grew dramatically starting on May 8; cases of the hemolytic–uremic syndrome appeared to peak on May 21 (median date of onset, May 21), and cases of Shiga-toxin–producing E. coli diarrhea appeared to peak on May 22 and 23 (Fig. 1), with a median date of hospitalization for hemolytic–uremic syndrome of May 24.

The three case patients with an onset before May 8 include two young children (one 4 years of age and the other 6 years of age), one of whom is not a resident of the outbreak area. Both are stx-positive, but serotypes are not available.

Cases of the hemolytic–uremic syndrome have been reported from all 16 states in Germany. The highest incidences are being reported from the northern states of Hamburg (10.1 cases per 100,000 population), followed by Schleswig–Holstein (6.7 cases per 100,000), Bremen (2.7 cases per 100,000), Mecklenburg–Vorpommern (2.2 cases per 100,000), and Lower Saxony (1.7 per 100,000) — the “northern Germany outbreak area.” The outbreak has been almost simultaneous in these areas. Most of the cases from other states can be linked to travel-related exposures in the northern Germany outbreak area. Figure 2 shows the incidence of the disease according to county of infection. Aside from two satellite clusters linked to restaurants in eastern North Rhine–Westphalia and southern Hesse, the area with high incidences (4 to 30 reported cases per 100,000 population) is centered around the city of Hamburg.

A total of 89% of the case patients in this outbreak are adults (i.e., persons older than 17 years of age). Among case patients 17 years of age or younger, the median age is 11.5 years.

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of diarrhea to the diagnosis of the hemolytic–uremic syndrome was 5 days (interquartile range, 4 to 6).

**CLINICAL INFORMATION**

Data on 141 patients, obtained at their first presentation to HUMC, were analyzed; 124 of the patients (88%) were adults. Among the adults, 66% were women, and the percentage was consistent across age groups; among the children, 50% were girls. No patient had a fever (defined as a temperature of at least 37.5°C) at the first presentation. Bloody diarrhea was reported less often in children than in adults (69% [9 of 13 children] vs. 20% [20 of 98 adults], P<0.001). Most patients did not have significantly elevated leukocyte levels (most were within the normal range; in some cases, counts were approximately 13,000 per cubic millimeter) or C-reactive protein levels (typically about 15 to 35 mg per liter [normal level, <5 mg per liter]). A total of 22 patients (16%) already met the criteria for the hemolytic–uremic syndrome at the time of presentation. Clinical and laboratory values in adults and children, stratified according to the presence or absence of the hemolytic–uremic syndrome, are summarized in Table 1.

Among the 135 patients who were followed prospectively, the Shiga-toxin–producing *E. coli* outbreak strain was detected in 59 (44%), and the hemolytic–uremic syndrome developed in 12 of these patients (20%; 95% confidence interval, 11

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**Figure 1. Epidemiologic Curve of the Outbreak.**

Shown are the number of cases of the hemolytic–uremic syndrome (HUS) and of Shiga-toxin–producing *E. coli* gastroenteritis, according to sex. Only cases with a known date of onset are included here — 748 of 810 cases of the hemolytic–uremic syndrome and 2166 of 2412 cases of Shiga-toxin–producing *E. coli* diarrhea.
Figure 2. Incidence of the Hemolytic–Uremic Syndrome According to County in Germany.

The incidence shown is per 100,000 population. A total of 810 cases have been detected so far in this outbreak. Cases are attributed to a particular county if that county was the probable site of infection.
to 33). Demographic and clinical characteristics at presentation did not differ significantly between patients with diarrhea in whom the hemolytic–uremic syndrome developed and those in whom it did not develop (Table 2). An examination of the platelet counts and creatinine and lactate dehydrogenase levels 5 days before through 2 days after the onset of the syndrome in 10 patients with the hemolytic–uremic syndrome (Fig. 4) indicates that the development of the hemolytic–uremic syndrome was sudden.

**Microbiologic Features**

The serotype of the Shiga-toxin–producing *E. coli* outbreak strain is O104:H4. The strain ferments sorbitol within 24 hours and is lactose-positive, beta-glucuronidase–positive, and subtilase-negative. The strain carries the gene for a Shiga-toxin 2 variant (stx2*). Other typical Shiga-toxin–producing *E. coli* genes such as stx1, eae, and ehx are missing. In addition, the pathogen possesses genes typical of enteroaggregative *E. coli*, such as attA, aggR, aap, aggA, aggC, located on a virulence plasmid (heat-stable enterotoxin EAST-1 negative). All outbreak strains are resistant to beta-lactam antibiotics (e.g., ampicillin) and third-generation cephalosporins and are partially resistant to fluoroquinolones (nalidixic acid). The strain is sensitive to carbapenems and ciprofloxacin. The outbreak strains produce an ESBL complex (CTX-M15) and beta-lactamase TEM-1. The National Reference Center has so far typed 439 isolates of this outbreak clone from 650 samples screened in local or regional laboratories for Stx production or presence of stx. Of the 60 isolates that have been analyzed thus far with the use of pulsed-field gel electrophoresis (4 from patients with the hemolytic–uremic syndrome and 56 from patients with Shiga-toxin–producing *E. coli* gastroenteritis), all have had indistinguishable patterns on pulsed-field gel electrophoresis.

**Discussion**

In this preliminary report, we describe the epidemiologic characteristics of a large outbreak of the hemolytic–uremic syndrome. There have been more than 800 incident cases of the hemolytic–uremic syndrome, predominantly affecting adults, in this outbreak since May 1, 2011. In addition, as of June 17, 2011, as many as 15 other countries, including the United States, have reported cases occurring among people who had traveled to northern Germany: 41 cases of the hemolytic–uremic syndrome (including one death) and 68 cases of Shiga-toxin–producing *E. coli* gastroenteritis. The current outbreak probably began on May 8 or 9; the three cases of the hemolytic–uremic syndrome in patients with an onset of gastroenteritis before these dates are atypical for the outbreak. In addition, the patient who had the first case of Shiga-toxin–producing *E. coli* gastroenteritis with confirmed serotype O104 infection had a disease onset on May 8.

To date, there are important differences between this outbreak and previous large outbreaks of Shiga-toxin–producing *E. coli* infection, such as the one that occurred in Japan in 1996, in which there were 121 cases of the hemolytic–uremic syndrome — all in children. First, the hemolytic–uremic syndrome represents a quarter of the ascertained cases, which is a much larger percentage than in other outbreaks. Second, the majority of the cases of the hemolytic–uremic syndrome (approximately 89%) have occurred in adults rather than in children, with the majority occurring in women. Third, the causative agent was a non–O157 Shiga-toxin–producing *E. coli* strain (O104:H4).

The outbreak strain combines the virulence properties of two different diarrhea-causing *E. coli* pathotypes: typical enteroaggregative *E. coli* and...
Shiga-toxin–producing *E. coli*. It has been speculated that the outbreak strain is a typical enteroaggregative *E. coli* strain that has acquired the bacteriophage encoding stx2a.18 Enteroaggregative Shiga-toxin–producing *E. coli* isolated from patients with the hemolytic–uremic syndrome have been described previously,19 albeit rarely. A similar Shiga-toxin–producing *E. coli* O104:H4 strain, with a different set of fimbriae, was isolated in 2001 from two siblings in Germany in whom the hemolytic–uremic syndrome had developed.20 Since typical enteroaggregative *E. coli* are isolated primarily from humans,21 the origin of this outbreak may not be zoonotic.

In this outbreak, the proportion of patients with outbreak cases in whom the hemolytic–uremic syndrome developed was 25%, despite public advice to patients to seek medical care (and laboratory testing) if they had bloody diarrhea—which probably led to a more complete ascertainment of gastroenteritis cases. Similarly, the hemolytic–uremic syndrome developed in 20% of prospectively observed patients with Shiga-toxin–producing *E. coli* diarrhea at a hospital in Hamburg. These proportions are higher than those in previous outbreaks12-17 and higher than the proportion (6%) ascertained through active surveillance of Shiga-toxin–producing *E. coli* O157:H7, the virulent prototype of Shiga-toxin–producing *E. coli*, in the United States.22 Taken together, these data suggest that the pathogen in the current outbreak is exceptionally virulent. Of note, the Shiga-toxin variant of the outbreak strain has previously been isolated in Germany only from the rare sorbitol-fermenting Shiga-toxin–producing *E. coli* O157:H−, a hypervirulent pathogen in children that is associated with high mortality.23 Another feature of the pathogen is the estimated median incubation period of 8 days for this outbreak, which is longer than the 3-day to 4-day incubation period reported for Shiga-toxin–producing *E. coli* O157:H7.13,24

### Table 1. Demographic and Clinical Characteristics and Laboratory Test Values of Patients Positive for Shiga-Toxin–Producing *E. coli* at First Presentation.∗

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 141)</th>
<th>Adults (N = 124)</th>
<th>Children (N = 17)</th>
<th>P Value†</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
<td>0.80</td>
</tr>
<tr>
<td>Mean</td>
<td>37</td>
<td>40</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2–87</td>
<td>20–84</td>
<td>22–87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex — no./total no. (%)</td>
<td>49/141 (35)</td>
<td>14/110 (13)</td>
<td>0/11</td>
<td>0.02</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Bloody diarrhea — no./total no. (%)</td>
<td>124/136 (91)</td>
<td>101/106 (95)</td>
<td>11/11 (100)</td>
<td>1.00</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Abdominal pain — no./total no. (%)</td>
<td>117/131 (89)</td>
<td>95/105 (90)</td>
<td>9/11 (82)</td>
<td>0.30</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Nausea — no./total no. (%)</td>
<td>33/97 (34)</td>
<td>23/77 (30)</td>
<td>4/8 (50)</td>
<td>0.30</td>
<td>3/4 (75)</td>
</tr>
<tr>
<td>Vomiting — no./total no. (%)</td>
<td>29/111 (26)</td>
<td>14/87 (16)</td>
<td>5/9 (56)</td>
<td>0.01</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>Temperature — °C</td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
<td>0.36</td>
</tr>
<tr>
<td>Hemoglobin — g/dl</td>
<td>13.5±2.1</td>
<td>14.2±1.4</td>
<td>10.8±2.4</td>
<td>&lt;0.001</td>
<td>14.1±1.6</td>
</tr>
<tr>
<td>Leukocytes — billions/liter</td>
<td>11.5±4.2</td>
<td>11.3±3.5</td>
<td>13.2±7.2</td>
<td>0.08</td>
<td>13.3±5.2</td>
</tr>
<tr>
<td>Platelets — billions/liter</td>
<td>215±88.4</td>
<td>245.3±52.5</td>
<td>88.3±92.8</td>
<td>&lt;0.001</td>
<td>297.4±39.4</td>
</tr>
<tr>
<td>Creatinine — mg/dl</td>
<td>1.4±1.9</td>
<td>0.8±0.2</td>
<td>2.6±1.9</td>
<td>&lt;0.001</td>
<td>0.7±0.3</td>
</tr>
<tr>
<td>Bilirubin — mg/dl</td>
<td>0.9±0.6</td>
<td>0.8±0.5</td>
<td>1.9±0.9</td>
<td>&lt;0.001</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>Lactate dehydrogenase — U/liter</td>
<td>410±569</td>
<td>196±95</td>
<td>890±433</td>
<td>&lt;0.001</td>
<td>230±42</td>
</tr>
<tr>
<td>C-reactive protein — mg/liter</td>
<td>18.2±30.0</td>
<td>15.0±27.0</td>
<td>30.2±32.2</td>
<td>0.06</td>
<td>46.0±65.7</td>
</tr>
</tbody>
</table>

∗ Plus–minus values are means ±SD. Data are for patients who presented to the Hamburg University Medical Center between May 19 and June 1, 2011. To covert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. HUS denotes the hemolytic–uremic syndrome.
† P values are for the presence versus the absence of the hemolytic–uremic syndrome within subgroups of children and adults.
At present, it remains to be elucidated why women are overrepresented among the cases of the hemolytic–uremic syndrome. No sex difference has been observed with respect to the risk of development of the hemolytic–uremic syndrome among a limited sample of patients with diarrhea who were prospectively followed at HUMC. Furthermore, it is unclear whether the atypical age distribution of cases in this outbreak primarily reflects the distribution of exposure or is attributable to the specific properties of this outbreak strain — or both. The outbreak strain lacks the intestinal adherence factor intimin (encoded by the gene \( eae \)), which might be of particular importance for virulence in children. The gene \( eae \) is found in the majority of Shiga-toxin–producing \( E. coli \) isolated from German children who have gastroenteritis (e.g., 85% of children younger than 3 years of age\(^25\)) and in 97% of these organisms isolated from children with the hemolytic–uremic syndrome in Germany and Austria.\(^26\) In contrast, the majority of Shiga-toxin–producing \( E. coli \) isolated from adults with sporadic cases of gastroenteritis lack \( eae \),\(^25\) and \( eae \)-negative strains have previously been isolated from adults with the hemolytic–uremic syndrome.\(^27\)

The most common clinical sign in adults was bloody diarrhea accompanied by abdominal cramps. The clinical presentation in adults differed from that in children. Bloody diarrhea occurred significantly more often in adults — irrespective of the presence or absence of the hemolytic–uremic syndrome — whereas vomiting was reported more frequently in children. Whether the high proportion of patients with bloody diarrhea reflects the characteristics of the strain or is a consequence of advice to the public to seek medical care in the case of bloody diarrhea is a subject for further investigation. Clinical symptoms such as abdominal pain, bloody diarrhea, and the frequency of loose stools did not differ between patients in whom the hemolytic–uremic syndrome developed and those in whom it did not. Changes in laboratory values, indicating renal failure and hemolysis, occurred quickly, often within 24 hours (Fig. 4). Daily laboratory testing of platelet counts and creatinine and lactate dehydrogenase levels appeared to be pivotal for the early diagnosis of the hemolytic–uremic syndrome, and these laboratory tests were more sensitive than were patient-reported symptoms and the physical examination. Indeed, several patients reported that they had begun to recover from bloody diarrhea several days after the initial presentation, at the same time as the onset of the hemolytic–uremic syndrome. For many reported cases, information on exact symptoms (e.g., diarrhea or bloody diarrhea) and additional microbiologic information are not yet available. Consequently, although the clinical picture of the hemolytic–uremic syndrome in adults appears to be very specific for this outbreak, among the

### Table 2. Demographic and Clinical Characteristics of Patients Positive for Shiga-Toxin–Producing \( E. coli \) (STEC) Who Were Followed Prospectively.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 59)</th>
<th>Without HUS (N = 47)</th>
<th>With HUS (N = 12)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>38.6±14.0</td>
<td>38.5±13.3</td>
<td>38.9±16.8</td>
<td>0.93</td>
</tr>
<tr>
<td>Male sex — no./total no. (%)</td>
<td>23/59 (39)</td>
<td>18/47 (38)</td>
<td>5/12 (42)</td>
<td>0.76</td>
</tr>
<tr>
<td>Reported fever — no./total no. (%)</td>
<td>4/55 (7)</td>
<td>4/46 (9)</td>
<td>0/9 (0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Bloody diarrhea — no./total no. (%)</td>
<td>48/58 (81)</td>
<td>37/46 (80)</td>
<td>10/12 (83)</td>
<td>0.87</td>
</tr>
<tr>
<td>Interval between onset of diarrhea and first presentation in STEC unit — days</td>
<td>4.1±4.7</td>
<td>4.0±5.0</td>
<td>4.1±3.3</td>
<td>0.98</td>
</tr>
<tr>
<td>Stool frequency — no. of stools/day</td>
<td>9.6±8.9</td>
<td>9.9±9.6</td>
<td>7.4±5.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Abdominal pain — no./total no. (%)</td>
<td>46/59 (78)</td>
<td>35/47 (74)</td>
<td>11/12 (92)</td>
<td>0.24</td>
</tr>
<tr>
<td>Vomiting — no./total no. (%)</td>
<td>11/59 (19)</td>
<td>7/47 (15)</td>
<td>4/12 (33)</td>
<td>0.15</td>
</tr>
<tr>
<td>Previous contact with other patients with STEC — no./total no. (%)</td>
<td>13/59 (22)</td>
<td>11/47 (23)</td>
<td>2/12 (17)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Data are for patients who were prospectively followed at the Shiga-toxin–producing \( E. coli \) (STEC) unit of the Hamburg University Medical Center between May 25 and June 6, 2011.
† P values are for the presence versus the absence of the hemolytic–uremic syndrome.
cases of Shiga-toxin–producing *E. coli* diarrhea, cases unrelated to this outbreak cannot be efficiently filtered out with the use of serotype information.

As of the time of this report, the German outbreak is not over, although case numbers are currently declining. Raw produce or salad condiments are suspected as the food vehicle. Investigations are ongoing.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the physicians and laboratory personnel, who are working under intense strain and yet are keeping up their notification requirements; local and state health departments for quickly passing on case data to the Robert Koch Institute; and epidemiologists in other countries for providing detailed travel and disease information regarding patients with travel-associated cases.
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