Escherichia coli O157:H7: Overview of Clinical and Epidemiological Issues

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ABSTRACT

Escherichia coli O157:H7 is an important and common human pathogen which causes diarrhea, bloody diarrhea (hemorrhagic colitis) and the life threatening post-diarrheal disorder, hemolytic uremic syndrome (HUS). Escherichia coli O157:H7 produces one or two potent cytotoxins, designated Shiga-like toxins (or verocytotoxins) I and II. While additional serotypes of cytotoxin-producing E. coli may cause human disease, E. coli O157:H7 is the most important such enteric pathogen in the United States. Epidemiologic data suggest that the incidence of hemolytic uremic syndrome is probably increasing. Until data emerge from controlled studies, conservative management of patients with HUS, E. coli O157:H7 should make prevention of human infection with this pathogen a high priority for the food industry.

Key Words: Escherichia coli O157:H7, hemolytic uremic syndrome, hemorrhagic colitis, Shiga-like toxins, verocytotoxins.

Escherichia coli O157:H7 is an important and common human pathogen which causes diarrhea, bloody diarrhea and the life-threatening postdiarrheal disorder, HUS (3,16,35). In North American clinical laboratories, which routinely screen for E. coli O157:H7, this organism is among the most frequently recovered bacterial enteric pathogen (13,20,22,38). Escherichia coli O157:H7 and the diseases it causes have been the topic of several recent comprehensive reviews (11,15,16,25). In this communication, we shall address several questions we are often asked about E. coli O157:H7, using data gathered from western Washington patients.

1. Do Shiga-like toxin producing E. coli that belong to serotypes other than O157:H7 cause human disease?

Multiple serotypes of E. coli contain genes encoding Shiga-like toxins (SLT) I and II (16), but the frequency with which these Shiga-like toxin producing E. coli (SLTEC) other than E. coli O157:H7 cause diseases is difficult to determine. Escherichia coli O157:H7 fails to ferment sorbitol within 24 h, and when plated on sorbitol-MacConkey agar the resulting colorless colonies provide a phenotype which is easily distinguishable from other fecal E. coli (21,44). Non-O157:H7 SLTEC are rarely sorbitol-negative and possess no other distinguishing biochemical traits, and are, therefore, difficult to identify without DNA homology studies (colony hybridization or the polymerase chain reaction) or cytotoxicity studies.

In North American and European series (4,9,14,23,27,37,42) E. coli O157:H7 has emerged as the predominant precipitant of HUS. In western Washington patients with HUS, E. coli O157:H7 was recovered from 24 (96%) of 25 patients from whom stool was obtained within six days of the onset of diarrhea, if E. coli O157:H7 was sought in these cultures (42). However, in series which have employed toxin detection methods to identify SLTEC, multiple additional serotypes have been incriminated as precipitants of HUS (3,12,17,19,36). These strains usually ferment sorbitol, have been overlooked using sorbitol MacConkey agar to identify candidate E. coli O157:H7, with serotyping to confirm the identity of the isolate. However, non-O157:H7 SLTEC have never been isolated in outbreaks of bloody diarrhea, causing some investigators to question their pathogenicity (1).

The role of non-O157:H7 SLTEC in causing diarrheal illness, which does not progress to HUS, is even more difficult to determine. Relatively few children with diarrheal illness undergo complete microbiologic examination, and few studies have used SLT gene or toxin detection methods to identify non-O157:H7 strains. Nonetheless, sporadic cases of diarrhea have yielded non-O157:H7 SLTEC, (15,31,43) and several groups have attempted to study the role of these organisms in epidemiologic studies. In Bangkok, the detection rate of non-O157:H7 SLTEC was similar in the stools of children with and without diarrhea, using DNA probes for SLT I or II on colony blots (6). However, other investigators have established stronger associations between non-O157:H7 SLTEC and human disease. Using a vero cell cytotoxicity assay, investigators in Argentina identified non-O157:H7 SLTEC more frequently in diarrheal stools than in the stools of children without diarrhea (19). In stools submitted for culture in Newcastle upon Tyne, United Kingdom, 28% of specimens without an identifiable patho-
coli contained a filterable cytotoxin specifically neutralized by antibodies to SLT I or SLT II, whereas such activity was not detected in controls (7). A similar study in Brussels identified cytotoxin-producing E. coli in 1.2% of stools submitted for culture with selected characteristics (the stool was liquid, grossly bloody, or the patient had hemorrhagic colitis or the HUS (33).

Several studies have been performed to identify the frequency with which stools presented for culture in North American microbiology laboratories contain non-O157:H7 SLTEC. In Calgary, Alberta, Canada, non-O157:H7 SLTEC were identified in 29 (0.6%) of 5,415 stools submitted for bacterial culture (31). In Vancouver, British Columbia, Canada, such strains were recovered from only 9 (0.1%) of 9,369 stools submitted for bacterial culture. Both of these studies employed vero cell cytotoxicity assays to identify non-O157:H7 SLTEC. In Seattle, Washington, 5 (1.1%) of 445 stools submitted to the Children’s Hospital and Medical Center Microbiology laboratory in a one-year prospective study were shown to contain non-O157:H7 SLTEC. In four of these five patients, these cytotoxin-producing organisms comprised the predominant coliform fecal flora (5). None of these five patients developed HUS, and only one had bloody diarrhea in contrast to the majority of patients with microbiologically confirmed E. coli O157:H7 infection in Washington State (20,29,42).

It is likely that a subset of SLTEC not belonging to serotype O157:H7 is capable of causing human disease, but the number of strains of E. coli containing cytotoxin genes in animals and food which are non-pathogenic is probably much greater (1). Bloody diarrhea may not be present, and the description of these SLTEC as enterohemorrhagic E. coli (EHEC) may not be appropriate (5). Because these non-O157:H7 strains lack an easily distinguishable phenotype such as the inability to ferment sorbitol, detection of these strains in stool specimens submitted for bacterial culture will probably remain the province of reference or research laboratories, which can perform DNA homology studies in cytotoxicity assays.

2. Is the incidence of human disease with E. coli O157:H7 increasing, or is it being better recognized by physicians and microbiologists?

Escherichia coli O157:H7 was first reported as a human pathogen in 1983 (35) and its increasingly frequent detection is due, in part, to the more widespread use of appropriate screening methods (e.g., sorbitol MacConkey agar) in clinical microbiology laboratories. Recognition of hemorrhagic colitis by physicians, and well publicized outbreaks of infection caused by E. coli O157:H7 (8,24) have also contributed to the apparently increased frequency of isolation with this pathogen.

Several investigators (23,39,40) have observed that the incidence of HUS has increased in incidence in King County, WA (which includes urban and suburban Seattle) and Minnesota. The rise in incidence of HUS began well before E. coli O157:H7 was described as a pathogen, or as the predominant precipitant of this disorder. Initial laboratory values in the hospital courses of patients studied were consistent throughout the periods analyzed. These constant indices of disease severity suggest that the increasing incidence was not merely caused by more frequent recognition of less severely ill children. Most of these cases were apparently sporadic, so the incidence data were not inordinately affected by recognizable outbreaks. Despite considerable interannual variation in its incidence, the authors of these studies concluded that the incidence of HUS was increasing, independent of ascertainment bias, between the early 1970s and the mid-1980s. Because HUS is a “sentinel” disease for human infection with E. coli O157:H7, these incidence data on HUS infer that human infections with E. coli O157:H7 are also increasing in frequency.

Screening of stools for E. coli O157:H7 was instituted by many laboratories in the Seattle area in the 1980s. We have subsequently observed aggressive investigation of bloody diarrhea with hemolytic and renal function testing during the week following the detection of E. coli O157:H7, in an attempt to diagnose HUS early. It is unlikely that such screening would identify many additional patients with severe HUS whose anemia, thrombocytopenia and anuria necessitates transfusion, dialysis and hospitalization. However, these tests might identify patients with mild HUS which might have been missed prior to physician awareness that E. coli O157:H7 can trigger this syndrome. For example, the laboratory records of 23 otherwise healthy patients with hemorrhagic colitis caused by E. coli O157:H7 infection between June 1985 and August 1987 were studied to determine the frequency of hemolytic or nephropathic derangements (26). Twenty-three, 14 and 75% patients with culture-proven E. coli O157:H7 infection who did not progress to overt HUS showed signs of evidence of intravascular erythrocyte destruction (abnormal erythrocyte morphology on peripheral blood smear), thrombocytopenia (platelet count less than 150,000/µl), or nephropathy (proteinuria, microscopic hematuria or pyuria), respectively. These abnormalities were manifest a mean of 4.6, 3.0 and 4.8 days after the onset of diarrhea, respectively (Table 1). Such abnormalities are similar to, but of lesser magnitude than, the hemolytic and nephropathic abnormalities observed in HUS.

In summary, we believe that available data suggests that HUS did increase in frequency in at least two North American populations during the past two decades. However, future studies of the incidence of HUS must take into account the severity of the illness being identified. Without determining the severity, it would be difficult to use HUS as a sentinel disease to follow secular trends in the incidence of E. coli O157:H7 infection in human populations, because ascertainment bias is introduced by physician awareness of microangiopathic potential sequelae to infection with E. coli O157:H7.

3. Can we halt the progression of E. coli O157:H7 infection from hemorrhagic colitis to hemolytic uremic syndrome?

Hemolytic uremic syndrome, the most severe complication of enteric infection with E. coli O157:H7, is diagnosed an average of 7 ± 2 (S.D.) days after the onset of diarrhea (42). The cascade of microangiopathic changes

4. Can we halt the progression of E. coli O157:H7 infection from hemorrhagic colitis to hemolytic uremic syndrome?
TABLE 1. Evidence for hematologic or renal injury in E. coli O157:H7 infection that does not progress to overt HUS.

<table>
<thead>
<tr>
<th>Laboratory abnormality</th>
<th>No. of patients evaluated</th>
<th>No. with Abnormal results (%)</th>
<th>Mean day of illness abnormalities observed (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte destruction on peripheral blood smear</td>
<td>22</td>
<td>5 (23%)</td>
<td>4.6 (1-11)</td>
</tr>
<tr>
<td>Thrombocytopenia (Platelet count less than 150,000/ml)</td>
<td>22</td>
<td>3 (14%)</td>
<td>3.0 (1-6)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>20</td>
<td>15 (75%)</td>
<td>4.8 (2-11)</td>
</tr>
<tr>
<td>Hematuria (1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pyuria (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria (1)</td>
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probably begins as soon as absorbed toxin affects endothelial cells lining the human host’s vasculature (28). Diarrhea and hemorrhagic colitis are almost always self-limiting, with very few patients experiencing long-term gastrointestinal symptoms. However, HUS, which occurs in approximately 5 to 10% of patients under age 10 infected with E. coli O157:H7, has a cumulative poor outcome rate (defined as percentage of patients with fatal HUS or chronic renal failure) of approximately 15%. Approximately 80% of patients with HUS require blood transfusions and half require dialysis. The one week interval between the onset of diarrhea and the diagnosis of HUS provides a potential opportunity to interrupt the pathologic cascade of E. coli O157:H7 infection. Antibiotics (to which most E. coli O157:H7 are sensitive), immune globulin directed against the toxin and orally administered toxin binders are all theoretical therapeutic interventions which might prevent HUS once enteric infection with E. coli O157:H7 is diagnosed.

Despite the appeal of these interventions, there are many reasons why these measures might fail. First, antibiotics might liberate more toxin from injured or killed E. coli O157:H7, making more toxin available for systemic absorption. In several studies, antibiotics either had no effect on the course of infection with E. coli O157:H7, (10,34) or were associated with a worse outcome (32). Second, pools of human immune globulins failed to neutralize the cytotoxicity of SLT II (2), which is common to almost all E. coli O157:H7 (30,41). Third, many patients with E. coli O157:H7 vomit (20,29) and orally administered toxin binders might achieve low concentrations in the colon, which is probably the site of the highest burden of E. coli O157:H7 in infected hosts. Finally, most patients do not seek medical attention until the diarrhea becomes bloody, which is generally on the second day of illness, and it is not until the third day of illness that a microbiologic confirmation of E. coli O157:H7 is made, assuming the appropriate cultures are obtained on presentation. By this time, approximately half of the interval between onset of enteric symptoms and the diagnosis of HUS has elapsed, and it is probable that toxin has already been absorbed from the gastrointestinal tract. Finally, the B subunit of SLT has structural homology to the alpha-2 interferon receptor, and such molecular mimicry might predispose to an autoimmune response to host cell structures (18).

When considering intervention strategies, the physician must realize that E. coli O157:H7 is a potentially fatal infection in otherwise healthy hosts, and that the present conservative management strategies of enteric infection with this pathogen leads to a successful outcome (a surviving patient without evidence of chronic renal failure) in almost all patients. Therefore, we urge that all therapeutic interventions be evaluated critically in prospective, controlled studies.

SUMMARY

Escherichia coli O157:H7 remains a common enteric pathogen of humans a decade after its initial description and association with the consumption of inadequately cooked ground beef. Diseases caused by this organism have probably increased in incidence during the past several decades, even prior to its recognition. Shiga-like toxin producing Escherichia coli other than E. coli O157:H7 might also cause human disease, though at present their epidemiological and clinical importance in North America is much less than E. coli O157:H7. Therapeutic interventions for the treatment of E. coli O157:H7 infection remain limited, and have not yet been validated by randomized, prospective controlled trials. The data presented above reinforce the importance of keeping E. coli O157:H7 out of the food chain, preventing its dissemination in the food manufacturing process, and cooking food of animal origin adequately to prevent infection at point of consumption.

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REFERENCES


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