A Review of the Pathophysiology and Treatment of Shiga Toxin Producing E. Coli Infection

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INTRODUCTION

The transmission of foodborne bacteria remains an important public health threat, because of the increased consumption of fresh vegetables and fruits, the challenges associated with producing large quantities of inexpensive foods, the increasing importation of foods from developing regions, and the increased consumption of foods in public restaurants (1). Of the more than 5.2 million cases of bacterial diarrhea that occur each year in the United States, 80% are a result of foodborne transmission (2). Shiga toxin–producing E. coli (STEC) is among the four most commonly reported bacterial enteropathogens in the United States and contributes to an estimated cost of $7 billion annually (3). STEC in particular, causes approximately 100,000 illnesses, 3,000 hospitalizations, and 90 deaths annually in the United States (2). This review article is intended to (i) discuss the epidemiology of the pathogenic E. coli O157:H7 strain; (ii) present its various clinical manifestations; (iii) identify current diagnostic methods; (iv) and outline current treatment strategies.

MICROBIOLOGICAL, EPIDEMIOLOGICAL, AND CLINICAL CONSIDERATIONS

The virulence of E. coli O157:H7 can partially be attributed to its ability to establish infection at low doses in humans. The vast majority of STEC infections present with hemorrhagic colitis as 91% of patients give a history of bloody diarrhea at some point during their illness (3). Significant morbidity and mortality secondary to infection is attributed to the development of hemolytic uremic syndrome (HUS). The diagnosis is generally established through a comprehensive history, physical exam, stool culture, PCR and endoscopic features. Given the overlapping clinical and endoscopic appearance of colonic ischemia and STEC, appropriate management can sometimes be challenging and ranges from supportive care to surgical intervention.

One of the most common complaints expressed to a gastroenterologist is diarrhea and/or rectal bleeding (Tables 1 and 2). The differential diagnosis is very broad with a wide spectrum of prognostic outcomes related to its etiology. E. coli O157:H7 was first recognized as a foodborne pathogen in 1982 during an investigation into an outbreak of hemorrhagic colitis associated with consumption of contaminated hamburgers (4). There have been over 200 different serotypes of STEC isolated, with only a few causing human illness and HUS. Several other potential factors (other than toxin production) have been proposed to explain this occurrence. The infectious dose of E. coli O157:H7 for humans is less than 100 organisms (5), which is low when compared to other enteric pathogens. Gastric acid is an important first barrier to ingested pathogens, and thus the reported resistance of the organism to gastric acid (6) helps to explain the low infectious dose. Under normal circumstances, non-pathogenic E. coli contributes to a protective intestinal microflora against pathogens. The low infectious dose of E. coli O157:H7 (7) is a major determinant of its ability to cause severe and epidemic disease, although the underlying mechanisms for this are not fully understood.
E. coli strains are classified based on their O and H antigens. The O antigen is determined by the repeating polysaccharide chains in the outer membrane. The H antigen is unique to the bacterial flagellum. After stereotyping the E. coli strain, the identification of shiga toxin production can further determine its virulence. Shiga toxin 1 (Stx1) is neutralized by antibodies against the Shiga toxin, whereas Shiga toxin 2 (Stx2) is not neutralized by antibodies against Shiga toxin but is neutralized by homologous antibodies (9).

Shiga toxin Escherichia coli transmission occurs through consumption of a wide variety of contaminated foods, including undercooked ground beef, unpasteurized juice, raw milk, raw produce (e.g., lettuce, spinach, and alfalfa sprouts), and also through ingestion of contaminated water (8). STEC causes approximately 100,000 illnesses, 3,000 hospitalizations, and 90 deaths annually in the United States, according to the last estimate in 1999 (2). Most reported STEC infections in the United States are caused by E. coli O157:H7, with an estimated 73,000 cases occurring each year (2).

**PRESENTATION**

Although STEC infections can cause non-bloody diarrhea, studies have shown that almost 63% of E. coli O157:H7 isolates come from visibly bloody specimens, and 91% of patients give a history of bloody diarrhea at
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some point during their illness (9). The clinical presentation is directly influenced by the degree of vascular endothelial damage, Shiga-like toxin production (which causes platelet aggregation), intravascular coagulation, and microangiopathic lesions with fibrin thrombi, all leading to hemorrhagic colitis. Clinical features independently associated with E. coli O157:H7 infection compared with other enteric pathogens included the absence of fever, leukocyte count greater than $10 \times 10^9/L$, and abdominal tenderness on physical examination (11).

Most of the literature emphasizes the most serious complication of this bacterial infection; hemolytic uremic syndrome (HUS) in the pediatric population and thrombocytopenic purpura in adults. Prior studies have demonstrated a clear progressive association of HUS with increasing white blood cell count in children (10). The risk associated with a WBC count has been defined as $>$13 $\times 10^9/L$ (11).

HUS is characterized by the triad of acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. It has been estimated that STEC causes at least 70% of post-diarrheal HUS in the United States. The requirement of dialysis has been reported in up to 50% of patients during the acute illness phase. HUS complicates 6% of STEC infections usually within 2 to 14 days after the onset of diarrhea (12). The development of HUS has also been reported to complicate up to 15% of STEC infections and has been described in 20% of cases in outbreaks (11,13,45). The mortality from HUS is between 3–17%, (14) but other studies have reported as high as 87% in the elderly (7). If the patient survives HUS, some reports indicate 5–10% of patients will have permanent and serious renal or neurologic sequelae after resolution of their infection (15). The average daily increase of lactate dehydrogenase (>1200 IU/L) and creatinine (>0.5 mg/dL) per day were associated with neurologic complications in pediatric patients with HUS (16). Seizure at onset was not a poor prognostic factor in pediatric patients (18). No positive correlation could be established between neuroimaging and long-term outcome (17).

**DIAGNOSIS**

Individuals with low gastric acidity (for example, patients status post gastrectomy or with pernicious anemia) are at a significantly higher risk of developing HUS than those with normal physiological gastric function (18). In select instances identifying the etiology of hemorrhagic colitis can be a challenging task given the broad endoscopic differential. Colonic ischemia and infectious colitis have many overlapping endoscopic features. An intricate relationship has been proposed identifying the involvement of E. coli in the pathogenesis of ischemic colitis in young patients (19). These two etiologies of hemorrhagic colitis should be differentiated as their treatment pathways can diverge. The diagnosis is often supported through history and identification of possible contributing risk factors and/or exposures. Colonic ischemia, which is the most common form of intestinal ischemia, comprises a spectrum of disorders ranging from reversible colopathy (submucosal or intramural hemorrhage) to fulminant colitis (21).

A study in Japan of 38 patients (with E. coli infection), who underwent colonoscopy within the first 3 days of illness onset, was able to confirm established endoscopic characteristics from prior studies (20). The study resulted in the development of a grading system of inflammatory findings (edema and erythema) as follows: (a) Grade 0 intact mucosa; (b) Grade 1 mild edema and sporadic erythema (with mild edema being defined as a Colonic lumen easily expanded by air with an indistinct vascular pattern); (c) Grade 2 moderate edema and semi-circumferential erythema (with moderate edema being defined as colonic lumen insufficiently expanded by air); (d) Grade 3 moderate edema and almost circumferential edema; (e) Grade 4 severe edema and diffuse, marked erythema (with severe edema being defined as a narrowing of the colonic lumen even with sufficient air through the colonoscope) (Figure 1).

In most patients with STEC, inflammatory preference was expressed in the cecum, ascending colon, and the right-transverse colon. These patients expressed a higher grade of inflammatory changes (grade 4). The inflammatory findings were less severe in the transverse and descending colon with an inflammatory grade of 3 or 2. In the sigmoid colon and rectum, the affected segments demonstrated an inflammatory degree of grade 1 (22). All patients manifested intact mucosa in the terminal ileum. Several previous studies have also indicated the inflammatory predominance of the right colon and
the presence of longitudinal ulcers. Biopsy specimens in EHEC patients revealed depletion of the mucosal epithelium, mucosal edema, intramucosal hemorrhage, and fibrin thrombi in the mucosal capillary.

Currently, the O157 STEC diagnosis is made primarily through stool culture. The incubation period between exposure to STEC and the onset of symptoms is three to four days (range one to nine days). Once colitis is established, fecal shedding of the bacteria may persist for up to 2 months, increasing the chance of person-to-person transmission (21). Patients infected with O157:H7 STEC also produce serum and salivary antibodies to their respective somatic or LPS antigens. (22,44) O157:H7 STEC can usually be easily distinguished from most E. coli strains comprising the normal intestinal flora, given its inability to ferment sorbitol on isolation media such MacConkey agar within 24 hours (23). The completion of confirmation procedures might take over an additional 24 hours. Polymerase Chain Reaction (PCR) assays to detect the stx1 and stx2 genes are used by many public health laboratories for diagnosis and confirmation (24,25,26). The time required to obtain PCR assay results ranges from 3 hours (if an isolate is tested) to 24–36 hours (if the specimen is first subcultured on an enrichment broth or plate). Simultaneous culture of stool for O157:H7 STEC and enzyme immunoassay testing for Shiga toxin is currently most effective for identifying STEC infections than the use of either technique alone (10).

Although rectal swabs can be utilized, swabs might not contain enough stool to culture for multiple enteric pathogens and to perform STEC testing. If rectal swabs are used to collect stool specimens for STEC testing, broth enrichment is recommended (10). Commercially available assays have not been validated for specimens collected by endoscopy or colonoscopy. If a laboratory chooses to use an assay for patient testing with a specimen other than that included in the manufacturer’s FDA approved package insert, under the Clinical Laboratory Improvement Amendments (CLIA) of 1988, that laboratory must first establish the performance specifications for the alternative specimen type (27).

Until recently, conventional PCR and real-time PCR approaches had been found to be useful techniques for detection of E. coli strains. However, PCR is technically demanding and requires several hours for a complete diagnosis. The presence of inhibitors in test samples reduces sensitivity of PCR when attempting to detect a target gene (28). Real-time PCR assay had many advantages over conventional PCR, including rapidity, lower contamination rate, higher sensitivity and easy standardization. However, tediousness and expense restrict its application to clinical laboratories (29). The development of a low-density macroarray for simultaneously testing for genes stx1, stx2, cae, ehxA, may provide an aid in the risk assessment of STEC virulence (30). A recent study found loop-mediated isothermal amplification to be a useful and powerful method for detection of E. coli O157:H7 strains, which can produce a rapid diagnosis in both commercial and clinical fields (31).

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TREATMENT

Given the overlapping clinical and endoscopic appearance of colonic ischemia (Figure 2) and STEC, appropriate management can be unclear. Both conditions warrant conservative management (bowel rest, attention to fluid and electrolyte replacement and correction of the precipitating cause) in less severe cases. When patients are more critically ill with abdominal pain, leukocytosis, massive bleeding and/or concern for fulminant colitis, surgery may be an important consideration. Given the concern for gram negative sepsis in critically ill patients, antibiotics are often used on presentation. Most authorities recommend the routine use of antibiotics in all patients with moderate or severe acute presentations of colonic ischemia (32). However, there is no clinical evidence of the beneficial effects of such therapy. This recommendation is based mainly on older experimental studies in which antibiotics reduced the severity and extent of bowel damage when given before an ischemic event (33).

The role of antibiotics in *E. coli* O157:H7 enteritis is still not firmly established. There has been a meta-analysis evaluation of the risk of hemolytic uremic syndrome after antibiotic use (Figure 3; Table 3) (34). This study did not show a higher risk of HUS associated with antibiotic administration, which had been previously implied by smaller studies. A larger randomized trial is still needed to conclusively determine whether antibiotic treatment of *E. coli* O157:H7 enterocolitis increases the risk of HUS (36). Another study regarding the detrimental or beneficial effects of antibiotics in the treatment of patients with *E. coli* O157:H7 has not resolved this issue (25). This review confirmed the presence of prior In Vitro studies showing most strains are susceptible to various antibiotics, although certain antibiotics, at sublethal concentrations may increase the release of Shiga-like toxin which has been associated with the development of HUS. No clinical studies have indicated that antibiotics are effective in reducing the duration of *E. coli* infection or duration of bloody diarrhea. However there have been studies supporting quinolones started within 3 days of infection onset (35) and fosfomycin within the first 2 days in children as agents preventing the development of HUS (36). Trimethoprim-sulfamethoxazole started within 3 or 4 days from onset of infection may be associated with an increased incidence of HUS, mainly in children, and/or longer duration of diarrhea and/or bloody diarrhea (37,38,39,40).

Postulated mechanisms to explain why antibiotics are not efficacious are that (a) they eliminate competing bowel flora leading to an overgrowth of *E. coli* especially if the strain is resistant to the antibiotic given; (b) they cause lysis or sublethal damage to infecting strains causing a release of the Shiga-like toxin (41); or (c) they induce the expression of the Shiga-like toxin gene (42).

Plasma exchange is not indicated for STEC-induced enteropathic HUS. Novel strategies are being designed for disease prevention or amelioration, including STEC-component vaccines (Stx, protective antigens), toxin neutralizers (Stx-neutralizing monoclonal antibodies [STmAAb], Gb3 mimics), and small molecules that block Stx-induced, pathogenic cellular pathways of cell activation/apoptosis (43).

CONCLUSION

Given the United States’ continued dependence on foreign food importation, potential *E. coli* contamination periodic outbreaks will remain a public health threat. All O157:H7 STEC isolates should be forwarded as...
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Figure 3. Relationship Between Antibiotic Therapy for *Escherichia coli* O157:H7 Enteritis and Risk of Hemolytic Uremic Syndrome. With permission from The Journal of American Medical Association [JAMA 2002;288(8):996–1001]. “Copyright © 2002 American Medical Association. All rights reserved.”

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Age Range of Patients, y</th>
<th>No. of Patients With E. coli O157:H7 Enteritis</th>
<th>No. of Patients Developing HUS</th>
<th>Antibiotics Used for Treatment</th>
<th>Interval Between Onset of Acute Diarrhea and Introduction of Antibiotic Therapy, d</th>
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<tbody>
<tr>
<td>Bell et al,11 1997</td>
<td>Retrospective cohort</td>
<td>&lt;16</td>
<td>278</td>
<td>36</td>
<td>Trimethoprim, ampicillin,</td>
<td>≤3</td>
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<td>Ikeda et al,12 1999</td>
<td>Prospective cohort</td>
<td>6–11</td>
<td>292</td>
<td>36</td>
<td>Fosfomycin</td>
<td>≤5</td>
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<tr>
<td>Slutsker et al,13 1998</td>
<td>Retrospective case–control</td>
<td>&lt;1–82</td>
<td>93</td>
<td>7</td>
<td>Sulfamethoxazole</td>
<td>≤3</td>
</tr>
<tr>
<td>Wong et al,14 2000</td>
<td>Prospective cohort</td>
<td>&lt;10</td>
<td>71</td>
<td>10</td>
<td>Trimethoprim-sulfamethoxazole, amoxicillin, cephalosporins</td>
<td>≤3</td>
</tr>
<tr>
<td>Proulx et al,15 1992</td>
<td>Prospective randomized</td>
<td>&lt;1–17</td>
<td>47</td>
<td>6</td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>7.4*</td>
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<tr>
<td>Cimolai et al,16 1994</td>
<td>Retrospective case–control</td>
<td>5 (Mean)</td>
<td>128</td>
<td>27</td>
<td>Not stated</td>
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<td>Ostroff et al,17 1989</td>
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<td>69</td>
<td>11</td>
<td>Trimethoprim-sulfamethoxazole, erythromycin, ampicillin, gentamicin sulfate, tetracycline</td>
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<td>Retrospective case–control</td>
<td>&lt;1–94</td>
<td>120</td>
<td>34</td>
<td>Ciprofloxacin</td>
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<td>Pavia et al,19 1990</td>
<td>Retrospective case–control and randomized trial</td>
<td>6–39</td>
<td>23</td>
<td>8</td>
<td>Sulfonamides, trimethoprim-sulfamethoxazone</td>
<td>≤3</td>
</tr>
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*Data are mean (range). With permission from The Journal of American Medical Association [JAMA 2002;288(8):996–1001]. “Copyright © 2000 American Medical Association. All rights reserved.”
soon as possible to a state or local public health laboratory for confirmation and additional molecular characterization (10). With early identification of infection, further efforts can be made to prevent recurrent outbreaks.

The vast majority of patients with STEC infection will recover with conservative management and without residual sequelae. Since STEC is a major contributor to a significant percentage of hemolytic uremic syndrome cases and demands public awareness during outbreaks, a new earlier diagnostic scoring system needs to be discovered. This system would combine history, risk factors, endoscopic appearance, and laboratory data. The clinician must be vigilant as clinical clues may present after initial evaluation. Daily laboratory studies should include CBC with differential (to identify hemolysis), electrolytes and renal function parameters. Once concern for hemolysis is established direct/indirect bilirubin, and LDH levels should be obtained. Early referral to hematology and nephrology can be life saving.

The role of antibiotics for the management of STEC infections still remains undecided after decades of debate and conflicting viewpoints in the literature. Nevertheless, the early use of antibiotics in critically ill patients with concern for sepsis is common practice. The clinician must have a high degree of clinical suspicion, but insight is limited without an accurate exposure history. More trials are needed to determine the most cost effective and reliable treatment protocols for this infection and its complications.

References
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19. Takashi Shigeno, Taiji Akamatsu, Kazuya Fujimori, Yoshiyuki Nakatsuji, Yoshiyuki Nakamura Evaluation of colonoscopic find
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