Hemolytic Uremic Syndrome Caused by Shiga Toxin–Producing Escherichia coli 0111

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Shiga toxin–producing Escherichia coli (STEC) was first discovered in 1977 and since has caused serious complications including the life-threatening condition of hemolytic uremic syndrome (HUS). While HUS is most common in children, adults and especially elderly patients experience a higher incidence of death and disability. Because the majority of HUS cases have been described in children, pediatric treatment options have been used to treat adult and elderly patients with HUS. More research regarding the treatment, risk factors, and prognosis of HUS in adults needs to be performed to ensure that optimal care is provided. The authors present a case series of 5 adults with HUS who were part of the largest outbreak of E coli 0111 reported in the United States. To date, there are no published cases of HUS secondary to E coli 0111 in adults. The authors also include a literature review of HUS secondary to STEC.

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Financial Disclosures: None reported.

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Submitted June 15, 2009; revision received December 14, 2009; accepted April 30, 2010.

Case Series

In August 2008, an outbreak of E coli 0111:NM occurred in Locust Grove, Oklahoma, affecting a total of 341 identified people—to our knowledge, the largest outbreak of E coli 0111 reported in the United States. Seventy-one patients were
hospitalized, 26 developed HUS, and 1 died. Analysis of affected patients’ stool samples by the Oklahoma State Department of Health revealed that Shiga toxin 1 (stx1) and Shiga toxin 2 (stx2) were produced by \textit{E. coli} 0111:NM.

We identified 3 men and 2 women (mean [standard deviation (SD)] age, 54.4 [9.2] years; range, 42-61 years) from two major hospitals in Tulsa, Oklahoma, as having HUS (Table 1). In these patients, HUS was defined by the presence of microangiopathic hemolytic anemia (MAHA; hemoglobin level <13.5 g/dL for men and <12 g/dL for women), thrombocytopenia, and acute renal failure (>0.3 mg/dL increase in the serum creatinine level between time of admission and diagnosis).

All patients also had a low haptoglobin level (ie, <26 mg/dL), presence of schistocytes on their peripheral blood smear, and prodromal bloody diarrhea, documented by historical report or positive occult blood in stool. Fever was not present from the time of admission to diagnosis in any patient.

On admission, serum creatinine levels ranged from 0.7 mg/dL to 1.6 mg/dL. The mean (SD) time from admission to diagnosis of HUS was 3.8 (1.6) days. Leukocytosis (WBC count >12,000/µL), was present in all 5 patients at the time of admission and in 4 patients at diagnosis. All patients had been treated with fluoroquinolones in the 2 weeks prior to HUS diagnosis.

Four of the 5 patients were treated with plasmapheresis. Of these 4 patients, 2 were also treated with hemodialysis. The patient who did not undergo plasmapheresis was treated with hemodialysis only (Table 2). The mean (SD) length of hospitalization was 21.6 (11.9) days (range, 11-42 days).

Renal recovery occurred in all patients and was documented on follow-up creatinine (Table 1), which is the creatine level documented from hospital discharge to up to 3 months after hospital discharge. The new onset of hypertension occurred in 3 of 5 patients, with the remaining 2 already having established hypertension prior to admission. Extrarenal manifestations other than colitis were documented in 2 patients (Table 2).

Comment
This case series illustrates the complexity of HUS and some of its widespread manifestations. Risk factors for progression to HUS noted in this series included an elevated WBC count and antibiotic use prior to HUS diagnosis. Unlike other outbreaks of \textit{E. coli} 0111 in Texas and Australia, this case series involved adults rather than children. While supportive therapy has proven to be beneficial in children with HUS, increased mortality and severity continue to be documented in adult patients.

The mortality rate in this subset of patients was much lower than that reported in other previously documented adult cases discussed in the present report. The average age of the patients in these studies may be a reason for the improved mortality rate.

The present case series highlights the challenges in identifying and managing HUS caused by STEC infection in adult patients. To provide a better understanding of HUS, we review its pathogenesis, clinical manifestations, diagnosis, treatment, and prognosis.

Pathogenesis
The central event in the pathogenesis of HUS is thought to be injury to the vascular endothelial cells. Examination of the capillaries in tissues from patients with HUS reveals swelling of vascular endothelial cells accompanied by a widening of the subendothelial space and intravascular fibrin.

### Table 1

<table>
<thead>
<tr>
<th>Demographic and Laboratory Characteristics of 5 Patients With Hemolytic Uremic Syndrome*</th>
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<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Temperature, °F</td>
</tr>
<tr>
<td>Prodromic Bloody Diarrhea</td>
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<tr>
<td>Schistocytes</td>
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<tr>
<td>Urine Output at Diagnosis, mL/d</td>
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<td>Haptoglobin at Diagnosis, mg/dL</td>
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<td>Admit Creatinine, mg/dL</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Discharge</td>
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<tr>
<td>Follow-up</td>
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<td>Hemoglobin, g/dL</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Discharge</td>
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<tr>
<td>Platelets, x 10^9/µL</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Discharge</td>
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<tr>
<td>LDH, U/L</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Discharge</td>
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<tr>
<td>WBC /µL</td>
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<tr>
<td>Diagnosis</td>
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<td>Discharge</td>
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*Patients were part of the 2008 *Escherichia coli* 0111:NM Outbreak in Locust Grove, Oklahoma, described in the present report.

**Abbreviations:** WBC, White Blood Cell
procoagulant cytokines. Lipopolysaccharides, which have Shiga toxins promote the production of proinflammatory and is the inhibition of protein synthesis. Shiga toxins are transported through which Shiga toxins cause disease. The toxins do not appear to carry equivalent risk of to 60% amino acid homology exists between stx1 and stx2 of STEC. The Shiga toxin produced by type 1 is almost identical to stx1 of STEC, yet only 55% to 60% amino acid homology exists between stx1 and stx2 of STEC. The toxins do not appear to carry equivalent risk of causing HUS. Serotypes that produce only stx1 have the lowest risk of causing HUS, while those that produce only stx2 have the highest risk. Strains that produce both stx1 and stx2 carry an intermediate risk.

Because STEC is noninvasive and rarely associated with bacteremia, it is generally believed that Shiga toxins must be absorbed through the intestine to cause disease. One mechanism through which Shiga toxins are thought to cause disease is the inhibition of protein synthesis. Shiga toxins are transported to target cells that have glycolipid globotriacylceramide (Gb3) receptors. The Shiga toxins bind to these receptors and are then internalized by receptor-mediated endocytosis. Within the cells, Shiga toxins halt protein synthesis by irreversibly inactivating ribosomes, which leads to cell death or severe cell damage. Consequently, endothelial swelling and detachment from the underlying basement membrane occur with secondary activation of both platelets and the coagulation cascade.

Lipopolysaccharides (LPS) elaborated by STEC have also been implicated in the pathogenesis of HUS. Both LPS and Shiga toxins promote the production of proinflammatory and procoagulant cytokines. Lipopolysaccharides, which have strong affinity for cell membranes, interact with cells to induce the production of cytokines and chemokines such as tumor necrosis factor (TNF-α), interleukin 6 (IL-6), and IL-8. Tumor necrosis factor upregulates the expression of Gb3 receptors on endothelial cells, and in conjunction with IL-1 has been found to in-crease specific binding sites for stx1 by 10- to 100-fold. Shiga toxins are transported by neutrophils to the kidney, where they are transferred and bound to receptors on target cells, glomerular endothelial cells, and tubular epithelial cells. Interleukin 8 increases the binding strength of leukocytes to endothelial cells, facilitating their infiltration into an area of inflammation.

The degree of leukocytosis may exacerbate the effect that IL-8 has on disease progression. Early in the course of these infections, prothrombotic coagulation abnormalities—similar to those observed several days later when HUS develops—are present, which suggest that these cytokines may prime the endothelium for the development of HUS. Cytokines and chemokines appear to stimulate glomerular endothelial cells to express Gb3 receptors, promoting a response to Shiga toxins and subsequently making endothelial cell surfaces more prothrombotic and adherent for neutrophils.

**Clinical Manifestations**
Approximately 90% of patients with HUS experience a diarrheal prodrome. The prodrome usually precedes HUS by 1 to 2 weeks and often resolves before the occurrence of HUS. The watery diarrhea is immediately followed by bloody stools in 74% to 95% of cases. Fever is reported in less than 30% of cases, which is interesting considering the infectious etiology of HUS.

Patients with HUS also experience abdominal pain, vomiting, and abdominal tenderness, prompting physicians to turn to surgical evaluation for initial diagnosis.

**Diagnosis**
Laparotomy and autopsy findings have revealed large-bowel edema, and in some cases small-bowel edema with areas of hemorrhagic necrosis and ulceration. Colonoscopy reveals diffuse severe inflammation with edema and friability, longitudi-nal ulcers, and findings somewhat consistent with ulcer-

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**Table 2**

<table>
<thead>
<tr>
<th>Hospitalization, Discharge, and Treatment Characteristics</th>
<th>Patient</th>
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<tr>
<td>Hospitalization, Discharge and Treatment Characteristics</td>
<td></td>
</tr>
<tr>
<td>No. of Days Hospitalized</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>No. of Days Between Admission and Diagnosis</td>
<td>21 17 11 17 42</td>
</tr>
<tr>
<td>Antibiotic Used Prior to Diagnosis</td>
<td>Levofloxacin Ciprofloxacin Levofloxacin Ciprofloxacin Ciprofloxacin</td>
</tr>
<tr>
<td>Plasma Infusion</td>
<td>No Yes No No No</td>
</tr>
<tr>
<td>No. of Plasmapheresis Therapies</td>
<td>7 0 4 7 1</td>
</tr>
<tr>
<td>No. of Hemodialysis Therapies</td>
<td>10 1 2 0 0</td>
</tr>
<tr>
<td>Hypertension on Discharge</td>
<td>New onset New onset Chronich Chronich New onset</td>
</tr>
<tr>
<td>Extrarenal Manifestations During Hospitalization</td>
<td>Hepatitis, neurologic colitis Colitis Colitis Colitis Pancreatic colitis</td>
</tr>
</tbody>
</table>

*Patients were part of the 2008 Escherichia coli O111:NM Outbreak in Locust Grove, Oklahoma, described in the present report.*
ative colitis.\textsuperscript{11,12} Biopsy results usually reveal thrombotic microangiopathy, which manifests more extensively in the mucosa and submucosa.\textsuperscript{2}

Parenterally administered Shiga toxins have caused colitis in animals, suggesting that bloody diarrhea may be caused in part by mesenteric ischemia initiated by circulating Shiga toxins rather than by direct STEC injury to the intestinal epithelium.\textsuperscript{6} Any area between the esophagus and the perianal area may be affected by HUS; more serious manifestations include severe hemorrhagic colitis, bowel necrosis, perforation, rectal prolapse, and intussusception.\textsuperscript{26}

The renal impact of HUS ranges from hematuria and proteinuria to severe renal failure and oligoanuria. In more than 60% of children with HUS, severe renal failure develops and necessitates dialysis. Approximately 20% of children who recover from severe renal failure develop end-stage renal disease after recovering from diarrhea-associated HUS.\textsuperscript{1,19,31} Both glomerular and extraglomerular arteriopathies result in patients with HUS. In regard to endothelial involvement, mainly preglomerular arterioles and capillaries are affected.\textsuperscript{19} Severe renal cortical necrosis demonstrates severe renal involvement and is associated more with pathology of the larger extraglomerular arterioles and the interlobular arteries than with smaller preglomerular capillaries and arterioles.\textsuperscript{19} Arterial hypertension due to volume overload or ischemia-induced activation of the renin-angiotensin system occurs in a majority of patients during the acute phase of HUS.\textsuperscript{2}

In addition to kidneys and intestines, nearly any organ can be affected by HUS. The brain is affected in up to 20% of children with HUS, and severe manifestations may include seizures, coma, stroke, hemiparesis, and cortical blindness.\textsuperscript{2} A direct correlation between central nervous system involvement and mortality has been identified in patients with HUS.\textsuperscript{22,28} Muscle involvement, indicated by elevated creatinine kinase or troponin levels, rarely occurs with HUS.\textsuperscript{1} Glucose intolerance has been associated with thrombotic microangiopathy restricted to the pancreatic islet cells.\textsuperscript{2} Hepatomegaly and elevated serum transaminase levels are also frequently found in patients with HUS.\textsuperscript{26}

Microangiopathic hemolytic anemia, a hallmark finding of HUS, is defined as nonimmune hemolysis with prominent red blood cell fragmentation. Laboratory test results for patients with hemolysis may include elevated lactate dehydrogenase levels, decreased haptoglobin levels, and the identification of schistocytes on peripheral blood smears. Microangiopathic hemolytic anemia is identified by means of a schistocyte count of greater than 1%, or 2 or more schistocytes in a microscopic field at 100× magnification.\textsuperscript{29,30} Thrombocytopenia is a diagnostic criterion for HUS; in patients with HUS, platelets are consumed as a result of thrombi in the microvasculature.\textsuperscript{2} Leukocytosis, another common hematologic manifestation, is associated with a worse prognosis, which may be related to the mechanisms of leukocytosis discussed earlier in this report.\textsuperscript{31}

Diabetes-associates HUS is diagnosed on the basis of the characteristic laboratory findings of MAHA, thrombocytopenia, and acute renal injury after a diarrheal prodrome. With diarrheal prodrome, absence of fever should raise suspicion that STEC could be the cause of dysenteric or bloody diarrhea. Patients with leukocytosis (determined with a complete blood cell count) after a diarrheal prodrome secondary to STEC may develop thrombotic microangiopathy. Renal biopsy may be helpful when diagnosis is uncertain and thrombocytopenia does not contraindicate biopsy because of bleeding risk. Some patients never develop renal impairment and are diagnosed as having incomplete, or forme fruste, HUS.\textsuperscript{25,32}

The diagnosis of STEC-mediated disease is typically confirmed by evaluating stool samples. Diagnostic approaches for STEC need to take into account the possibility that the organism identified is a pathogen and whether that organism has a reasonable likelihood of precipitating HUS.\textsuperscript{8} Because of the high prevalence of \textit{E. coli} O157:H7, all patients with bloody diarrhea should be evaluated for this strain by means of a stool culture on sorbitol–MacConkey agar. To evaluate for the possible false-negative results of this test and to identify non-O157:H7 STEC, a Shiga toxin assay should also be performed.\textsuperscript{6,31} Unlike other STEC, serotype O157:H7 is unable to ferment sucrose.\textsuperscript{3} Thus, plating this organism on sorbitol–MacConkey agar will reveal white colonies in about 50% of stool samples. Likewise, it will fail to identify half of \textit{E. coli} O157:H7 cases and all cases of non-O157:H7.\textsuperscript{3} Shiga toxin assays have a relatively good diagnostic sensitivity and diagnostic specificity and are tested by latex agglutination, enzyme-linked immunosorbent assay, and polymerase chain reaction.\textsuperscript{6,33} Even if collected in the appropriate enrichment broth, not all Shiga toxin–positive specimens will produce a successful culture because diagnosis of HUS usually occurs several days after the onset of diarrhea, when the number of pathogens in the stool is decreasing.\textsuperscript{33}

Serologic testing is another strategy for diagnosing STEC. Seven to 10 days after bacterial LPS enter the bloodstream, an antibody response occurs. According to findings in previous studies, the presence of IgG and IgM antibodies to \textit{E. coli} O157 is a good indicator of recent infection.\textsuperscript{10} IgM antibodies to STEC LPS have a 95% and 99% diagnostic sensitivity and specificity, respectively. Antibody levels may remain elevated for up to 11 weeks—an advantage over more time-sensitive stool cultures. In addition, serologies for antibodies to LPS antigens of different STEC strains can help confirm diagnosis when stool culture results are negative.\textsuperscript{32,34}

**Treatment**

Currently, the progression of hemorrhagic colitis to HUS cannot be prevented. Increased expansion of fluid volumes by means of intravenous rehydration and maintenance of fluids during the diarrheal phase has been reported to provide nephroprotection, which may attenuate but will not prevent renal injury.\textsuperscript{8} An observational study\textsuperscript{35} of 29 patients with HUS analyzed the association between fluid replenishment and
severity of renal failure. More vigorous fluid replenishment during the diarrheal phase of the illness suggested less severe renal involvement.

Fluid management is determined by the intravascular volume state and renal function of the patient. At the first sign of hypertension or cardiopulmonary overload, fluids should be restricted and reassessed. Dialysis therapy may be indicated for volume-overloaded patients unresponsive to diuretics. However, there is no evidence that dialysis affects clinical outcome, and indications for dialysis in HUS are similar to those for other forms of acute renal failure. Patients with HUS can also become profoundly anemic, and transfusion may be a viable treatment option to avoid cardiovascular and pulmonary collapse. Approximately 80% of patients with typical HUS require red blood cell transfusions. Because platelets may contribute to the formation of microthrombi and promote tissue ischemia, platelet transfusions are discouraged unless patients have severe hemorrhaging or are undergoing invasive procedures.1,5,6,19,32,36

Two treatments once thought to be beneficial in the management of the diarrheal phase of the disease are now known to increase the risk of progression to HUS. The first, the use of antimotility agents or narcotics, should be avoided for all patients suspected of having STEC infection because these agents have been associated with an increased risk of HUS and associated neurologic complications.6 In a retrospective review of 278 children with HUS, the use of antimotility agents was associated with a 190% increased risk of developing HUS.

The second treatment, once thought to be beneficial but now recognized as harmful in the management of HUS, is the use of antibiotics. Both retrospective and prospective observational studies report an increased risk of HUS with administration of antibiotics during the diarrheal phase of illness. In 2000, a multicenter, prospective study of 71 children with confirmed STEC infection showed a 17.3-fold increased risk for development of HUS with early antibiotic therapy. In a 1993 outbreak in Washington State, antibiotics administered early in illness were not associated with a diminished risk of developing HUS.37 It is suspected that antibiotics cause induction of bacteriophages—on which Shiga toxin genes are located—which subsequently results in increased toxin production.36,11,32 Fluoroquinolones have been reported to induce the release of Shiga toxins from E coli O157:H7 in vitro.38 However, a retrospective analysis30 of an outbreak in Japan revealed that fluoroquinolone exposure for 5 days eradicated E coli O157:H7 in children. The role of fluoroquinolone therapy in causing and managing HUS needs to be explored.

While controversial, plasmapheresis would likely remove Shiga toxins and proinflammatory cytokines suspected to initiate and perpetuate the microvascular process that leads to HUS.12 The three main indications for plasmapheresis in patients with STEC is its toxin size (ie, >15 kDa), its acute toxicity, and its resistance to conventional therapy. In 2003, the American Society of Apheresis assigned plasmapheresis as a category III treatment option for patients with HUS. This category level indicates that the benefit of treatment is not clearly defined.39 Plasmapheresis may be associated with potentially critical complications, including severe anaphylactoid reactions, arrhythmias, and hypotension. Less severe complications include citrate-induced hypocalcemia and citrate-induced metabolic alkalosis.

While currently there are no randomized controlled trials being performed to evaluate the effectiveness of plasma exchange in adult HUS patients, multiple reports have suggested plasma exchange may be an effective treatment option for adult patients with HUS. In 1996, an outbreak of STEC O157:H7–related HUS demonstrated the potential efficacy of plasma exchange in improving survival rates.12 In this outbreak, 83% of those who did not undergo plasma exchange died, whereas only 31% of those who did receive plasma exchange died.12 In another case series of adult patients who presented with overt bloody diarrhea, 17 of 21 patients responded to plasma exchange treatment.15 Plasma exchange has been used to treat children with HUS in which the central neurologic system was affected. However, the outcome of this treatment option has been inconclusive.1 One report40 suggested plasma exchange shortened the duration of acute renal failure in children and led to better long-term renal function.

Many approaches to treatment of patients with HUS have been unsuccessful. For example, there is no current evidence that anticoagulants, prostacyclin, steroids, or intravenous immunoglobulin are of value in the treatment of HUS.19 Two prospective controlled trials36 indicated that plasma therapy may limit short-term renal lesions caused by HUS but does not affect long-term renal outcome and survival. The orally administered toxin binder Synsorb Pk (Synsorb Biotech Inc, Calgary, Alberta, Canada), which was offered as an investigational drug in an E coli outbreak in Milwaukee, Wisconsin, in 2000, failed to show improvement in clinical outcomes for children with HUS.1 Certain treatment options for HUS still lack support in terms of study results and FDA approval or are currently under investigation. The newest compound, DAISY, is a decavalent globotrioside glycolipid–related Shiga toxin receptor analogue that inhibits the activity of stx1 and stx2 by preventing the adhesion of Shiga toxin to target cells. When administered intravenously, DAISY has been shown to protect mice.1 It has been suggested that plasminogen-activating inhibitor type 1 may be a circulating factor inhibitor of fibrinolysis in HUS.41 In one study, normalization of plasminogen-activating inhibitor type 1 was associated with improvement in renal function.42 A clinical trial designed to test the effectiveness of neutralizing anti–Shiga toxin antibodies in preventing HUS has been initiated at McGill University in Montreal, Quebec, Canada.3 A baboon model of Shiga toxin–mediated injury that reproduces human disease has also been developed.3 This model has provided insight to the likelihood that prostacyclin is involved in the pathophysiologic processes of HUS and that elevated levels of von Wille-
brand factor is central to the pathogenesis of HUS. Another study has shown that stx2 is bound to polymorphonuclear leukocytes in patients with HUS and may provide further insight into diagnosis and therapy. It is likely that the amount of toxin that enters the systemic circulation is a critical factor in determining which patients will develop HUS and other systemic manifestations. While the amount of Shiga toxins necessary for HUS progression remains unknown, the described techniques or other diagnostic options may make this information available and quantifiable in the future.

Prognosis
Spontaneous resolution of HUS occurs in most affected children 1 to 2 weeks after the onset of diarrhea. Renal function will usually resolve after hemoglobin and platelet levels return to baseline. The mortality rate in children who develop HUS has been estimated to be 5%, with an equal percentage developing either end-stage renal disease or severe neurologic sequelae. In a retrospective study of 17 children who died of HUS, 15 died during the acute phase of HUS. Of these 15, 8 died of disease involving the central neurologic system. Hyperkalemia, congestive heart failure, and pulmonary hemorrhage accounted for the other deaths. A meta-analysis of 3476 patients suspected of having diarrhea-associated HUS also revealed an increased mortality rate and occurrence of end-stage renal disease in those patients with severe neurologic manifestations.

The glomerular filtration rate typically returns to normal in most children. However, some patients have demonstrated a persistent 10% to 20% decrease in renal blood flow, which may suggest subclinical loss of nephron function. Two reports with mean follow-ups of 9.6 and 8.5 years have suggested an increased incidence of chronic renal sequelae as evidenced by hypertension, proteinuria, and/or a decline in glomerular filtration rate. These comorbidities occurred in up to one-third of children with prolonged initial disease defined by anuria lasting more than 8 days or oliguria lasting more than 15 days. The meta-analysis previously described demonstrated that death or end-stage renal disease occurred in 12% of children with diarrhea-associated HUS, and 25% of survivors developed long-term renal sequelae. Approximately 10% of those with renal impairment have both proteinuria and decreased glomerular filtration rate. This combination may place patients at high risk for loss of renal function and eventual end-stage renal disease due to hyperfiltration injury.

The course and prognosis of HUS has been suspected to be different between adults and children. Studies have shown that children with HUS exhibit a better response to dialysis and have decreased mortality rates compared to adults. In 1996, an E coli O157 outbreak in central Scotland primarily affected adults. Adults developed neurologic and cardiovascular complications before the onset of oliguria and 45% with HUS died. In September 1985, a severe outbreak of E coli O157:H7 occurred within a nursing home in Ontario, Canada, and 11 of 12 patients with HUS died. The patients in this outbreak were older and had more comorbidities than the patients in the central Scotland outbreak.

Conclusion
STEC is a serious health concern because of its propensity to cause outbreaks, hemorrhagic colitis, and potentially fatal HUS, as described in the present report. With improved diagnostic techniques, recognition of non-O157:H7 STEC will likely improve and allow earlier recognition and interruption of outbreaks. Prospective studies that evaluate adult treatment need to be further emphasized.

Improved monitoring for HUS in the United States presents an opportunity to help understand and control this potentially devastating illness. State health departments have more recently developed registries for both adult and pediatric patients identified with HUS. This database of information will assist with identifying risk factors that predispose HUS and will enable the monitoring of treatment and outcomes. Multiple other developments in the realm of HUS research are also under way, and the medical community anxiously awaits their results.

References
CLINICAL PRACTICE


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