Hemolytic Uremic Syndrome: An Emerging Health Risk

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Hemolytic uremic syndrome is caused primarily by Shiga toxin–producing *Escherichia coli* O157:H7. The most common cause of acute renal failure in children, hemolytic uremic syndrome also can occur in adults. Characteristic features of the syndrome are microangiopathic anemia, thrombotic thrombocytopenia, and renal failure. Although the presentation of this syndrome is diverse, the classic prodromal illness is bloody diarrhea following ingestion of hamburger meat contaminated with *E. coli* O157:H7, the most common mode of infection in the United States. Children with hemolytic uremic syndrome generally present with gastroenteritis complaints (e.g., abdominal pain or tenderness, nausea or vomiting, fever, anemia); affected adults may be asymptomatic. Complications from hemolytic uremic syndrome can include intussusception, chronic renal failure, and seizures in severe cases. Because an incubation period of approximately one week occurs between the start of diarrhea and the onset of hemolytic uremic syndrome, physicians should maintain a high index of suspicion; early laboratory testing is important to diagnose and manage this syndrome. Obtaining a complete blood count and stool culture and performing Shiga toxin testing are the first of a series of tests that may help diagnose hemolytic uremic syndrome. (Am Fam Physician 2006;74:991-6, 998.

▶ **Patient information:** A handout on hemolytic uremic syndrome, written by the author of this article, is provided on page 998.

Hemolytic uremic syndrome is the most common cause of acute renal failure in children, and the incidence of this syndrome in children is increasing worldwide.[1] First identified in 1955, hemolytic uremic syndrome affects children and adults.[2] Attempts to link it to only underdeveloped countries are unsupported because outbreaks occurred in parts of Europe beginning in 1992, the United Kingdom in 1994,[3] the United States in 1996,[4,5] and Japan in 1996.[1,6,7]

Etiology

Hemolytic uremic syndrome can be classified into two types, depending on the presence of a diarrheal prodrome. Diarrhea-positive hemolytic uremic syndrome is associated strongly with Shiga toxin–producing *Escherichia coli* (STEC). Diarrhea-negative hemolytic uremic syndrome is seen in adults and occurs sporadically.[8] Diarrhea-associated hemolytic uremic syndrome is more common in children. It can be endemic, linked to a common source of infection, and result in bloody diarrhea. Precipitating factors can include familial predisposition (e.g., factor H deficiency),[2] infections (e.g., *E. coli, Streptococcus pneumoniae*), pregnancy, or medications such as cyclosporine (Sandimmune)[9] *(Table 1*[10]*). E. coli* O157:H7 is responsible for most of the diarrhea-associated hemolytic uremic syndrome in children in North America, but other strains that are more difficult to detect also have been implicated.[4-7]

Diarrhea-associated hemolytic uremic syndrome is more common in children.

Pathophysiology

The pathophysiology of hemolytic uremic syndrome is not well understood. Proinflammatory (elevated interleukin-8 and tumor necrosis factor α)[1] and prothrombotic changes in the coagulation pathway, along with damage to the endothelial cells, result in end-organ damage.[11] Results of the latest studies show damage to mesangial cells, renal tubular epithelial cells, monocytes, and monocytes-derived cell lines in addition to the endothelial cell.[1]

Most strains of *E. coli* are harmless; however, enterohemorrhagic *E. coli* can release

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
All stools should be cultured for STEC when the index of suspicion is high for *Escherichia coli* O157:H7.	C	12, 29
Do not treat with antibiotics or antidiarrheals while the patient is in the diarrheal stage.	C	25, 26
Because hemolytic uremic syndrome is a reportable disease, local public health officials should be notified.	C	23

STEC = Shiga toxin–producing E. coli.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 906 or http://www.aafp.org/afpsort.xml.

Shiga toxins that attach to and damage the endothelial lining of the intestine, resulting in hemorrhagic and ulcerative lesions.[2] Subsequently, the Shiga toxins gain access to the circulatory system. By attaching to the Gb3 receptors, protein synthesis is inhibited, resulting in cell injury and death; this causes microangiopathic hemolytic anemia, thrombocytopenia, and deposits of microthrombi.[1] These ischemic changes manifest as damage to various organs, especially the kidneys.[2]

E. coli O157:H7 is believed to cause more than 80 percent of the STEC infections that lead to hemolytic uremic syndrome.[12] This microorganism is not a normal part of the human intestinal flora[13] but is present in the intestines of 1 percent of healthy beef cattle; the meat can become contaminated during the slaughter and processing of the animal. *E. coli* also has been found to contaminate other food products *(Table 2)*. The most common form of transmission to children in the United States is ingestion of undercooked ground beef containing *E. coli* bacteria. *E. coli* bacteria also may be transmitted by contact with persons who inadequately wash their hands, resulting in fecal and oral contamination and transmission.[14]

TABLE 1
Types and Causes of Hemolytic Uremic Syndrome

Infection induced (typical)
Bacteria (e.g., *Escherichia coli* O157:H7, *Streptococcus pneumoniae*) or virus
Genetic, drug induced, idiopathic (atypical)
Exposure to toxins (e.g., cyclosporine [Sandimmune], tacrolimus [Prograf], radiation)
Hereditary factors
Human immunodeficiency virus
Systemic conditions (e.g., lupus, cancer, glomerulonephritis, pregnancy)

Information from reference 10.

Epidemiology

Hemolytic uremic syndrome primarily occurs in children one to 10 years of age,[1,15] with an average annual incidence of one to three cases per 100,000 children[9] and a survival rate of nearly 95 percent. Some studies indicate that rural populations are more at risk than urban populations,[14,16] and the incidence is higher in warmer months, peaking from June to September.[13] Occurrences may be sporadic or present as an outbreak. A study conducted in the United Kingdom, in which confections intentionally were artificially contaminated with *E. coli* O157:H7, showed that the Shiga toxin–producing strains could survive for as long as one year, depending on storage conditions.[17]

Three to 15 percent of persons who have STEC with diarrhea can develop hemolytic uremic syndrome.[18] Young children and older persons with altered immune response,[19] as well as persons who have been in contact with infected farm animals, are particularly

TABLE 2
Reported Sources of Shiga Toxin–Producing *Escherichia coli*

Food items
Alfalfa sprouts
Apple juice/cider, unpasteurized*
Deer meat, undercooked
Goat's milk, unpasteurized
Ground beef, undercooked*
Leaf lettuce
Meat, cold cooked sliced meat
Milk, unpasteurized*
Radish sprouts
Sausages, particularly beef, undercooked
Environmental sources
Fecal-contaminated lakes
Nonchlorinated municipal water supply
Petting farm animals
Unhygienic person-to-person contact

**—Most commonly reported sources.*

vulnerable. In addition to age, risk factors associated with hemolytic uremic syndrome include bloody diarrhea, fever, and elevated white blood cell count and C-reactive protein levels.[6] The use of antibiotics or antimotility/antidiarrheal and antimicrobial agents in the early stages of diarrhea has been shown to increase the risk of hemolytic uremic syndrome because the gut is exposed to a greater number of toxins for a longer period as intestinal motility slows.[13,20]

Clinical Characteristics

The classic triad of features for hemolytic uremic syndrome consists of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure.[21-23] Children infected with *E. coli* O157:H7 are symptomatic; infected adults may be asymptomatic. The incubation period for *E. coli* O157:H7 is usually three to four days; however, the incubation also can range from just one day to eight days.[13] Typical hemolytic uremic syndrome usually develops after a prodrome of diarrhea. Clinical features identifying patients at high risk for hemolytic uremic syndrome are vague and may mimic common gastroenteritis, including bloody diarrhea occurring from three days to more than two weeks before hemolytic uremic syndrome is diagnosed.[2] Additional symptoms include nonbloody diarrhea, abdominal cramping, and nausea or vomiting. Fever may be low grade or even absent. Ten percent of cases are associated with rectal prolapse with colitis.[2]

Hemolytic uremic syndrome cannot be diagnosed without evidence of hemolytic anemia. Hematologic findings include destruction and fragmentation of erythrocytes that result in microangiopathic hemolytic anemia. This develops in all patients within a day or so of contamination and may result in respiratory and cardiovascular compromise. Mean hemoglobin concentration of 6 g per dL (60 g per L) is common and requires red blood cell transfusion.[2] Ninety-two percent of patients with hemolytic uremic syndrome develop thrombocytopenia, which results from entrapment of platelets in the organs.[2] Clotting times are normal, and petechiae and purpura are uncommon features of hemolytic uremic syndrome.[22] Platelet transfusion is not recommended because it could exacerbate the thrombotic process; however, risks and benefits should be considered when platelet transfusion is indicated (e.g., invasive vascular procedure, active bleed).[2]

Acute renal failure results when microthrombi are deposited in kidney parenchyma. This manifests in the form of hypertension associated with oliguria and anuria, which are early signs of acute renal failure.

The central nervous system is another organ system that could become involved. Thirty-three percent of patients with hemolytic uremic syndrome experience neurologic complaints such as irritability, seizures, and altered mental status.[2]

Differential Diagnosis

The differential diagnosis of hemolytic uremic syndrome includes viral or bacterial gastroenteritis, septicemia with disseminated intravascular coagulation, and thrombotic thrombocytopenia *(Table 3)*. Diarrhea

Characteristic features of hemolytic uremic syndrome are microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure.

TABLE 3
Differential Diagnosis of Hemolytic Uremic Syndrome

Condition	*Signs/symptoms differentiating from hemolytic uremic syndrome*
Acute abdomen	Abdominal pain worsening with time, guarding and rigidity present
Acute gastroenteritis	Mild abdominal pain, abdominal tenderness, nonpainful defecation
Appendicitis	Absence of anemia or thrombocytopenia, pain in right lower quadrant
Colitis	Afebrile, elevated white blood cell count in stool sample
Disseminated intravascular coagulation	Low fibrinogen level, prolonged prothrombin time, prolonged partial thromboplastin time
Inflammatory bowel disease	Diarrhea or constipation, abdominal pain, nausea, weight loss, high-grade fever
Intussusception	Currant-jelly stool, episodic cramping, abdominal pain
Lupus	Absence of antiplatelet antibodies, presence of antiphospholipid antibodies
Thrombotic thrombocytopenia	Presence of neurologic abnormalities

or abdominal cramps and absence of fever can be mistaken for inflammatory bowel disease, ischemic colitis, or intussusception. Additionally, abdominal pain and tenderness could mimic appendicitis or an acute abdomen.

Laboratory Evaluation

Laboratory testing can be used to secure a diagnosis of hemolytic uremic syndrome *(Table 4)*. Findings of hemolysis and thrombocytopenia on a complete blood count are required to establish the diagnosis. Many patients will no longer be shedding STEC by the time the clinical features of hemolytic uremic syndrome begin, but obtaining stool cultures is important because verifying the presence of STEC in patients with this syndrome has significant public health implications. Hemolytic uremic syndrome is a reportable disease; therefore, local public health officials should be notified.[23]

Management

Typical hemolytic uremic syndrome is a self-limiting disease with spontaneous recovery, although close monitoring and treatment of symptoms are essential. Because hemolytic uremic syndrome has a wide spectrum of presentations, supportive therapy (e.g., good nutrition, close monitoring of fluid and electrolyte status) is crucial for a good outcome. Recent studies indicate that the amount of parenteral hydration given to a patient before the development of hemolytic uremic syndrome, especially the amount of sodium, is crucial in preventing anuria and, ultimately, dialysis.[11]

Strict fluid balance monitoring is important in detecting early renal failure. If failure develops, it should be handled aggressively[24] by starting renal replacement therapy (e.g., peritoneal dialysis, hemodialysis).[15] Hypertension is treated traditionally with antihypertensives and diet.

Antibiotics and antimotility agents are not recommended as treatments for hemolytic uremic syndrome during the diarrheal stage of the disease. Studies of antibiotic usage in children with *E. coli* O157:H7 infections show an increased risk of complications from hemolytic uremic syndrome.[25,26] One

TABLE 4
Common Laboratory Abnormalities in Hemolytic Uremic Syndrome

- Anemia: hemoglobin count of 5 to 9 g per dL (50 to 90 g per L)
- Azotemia
- Decreased haptoglobin
- Elevated C-reactive protein level
- Hematuria on urinalysis
- Hemolysis on peripheral smear: burr cells, helmet cells
- Increased L-lactate dehydrogenase level
- Leukocytosis
- Negative Coombs' test
- Proteinuria on urinalysis
- Reticulocyte count moderately elevated
- Stool culture positive for Shiga toxin–producing *Escherichia coli* O157:H7
- Thrombocytopenia: platelet count less than 150,000 per mm^3

study reported that using antibiotics to treat children testing positive for *E. coli* O157:H7 increased their risk of developing hemolytic uremic syndrome.[26] Additionally, some children who were diagnosed with *Shigella dysenteriae* type 1 and treated with ampicillin developed hemolytic uremic syndrome.[25]

Serial monitoring of the hematocrit and platelet count is important. Currently, platelet transfusion is controversial because it can worsen the thrombotic process.[27] However, transfusion of red blood cells may be needed to aggressively correct anemia, which can deteriorate the patient's condition and further complicate the picture by causing respiratory and cardiovascular compromise.

Modalities such as plasmapheresis, antithrombotic agents, steroids, and Shiga toxin–binding agents have proved ineffective and remain controversial.

Complications

Complications of hemolytic uremic syndrome can involve the renal, gastrointestinal, or neurologic systems *(Table 5)*. The most severe renal complication is chronic renal failure. Approximately 12 percent of patients who contract hemolytic uremic syndrome either develop end-stage renal disease or die.[28] Additional complications include hypertension, proteinuria, and renal impairment. However, extra-renal complications such as pancreatitis (which may lead to diabetes), cerebral involvement, cardiomyopathy, and gastrointestinal involvement also may occur.

Approximately 10 percent of patients with hemolytic uremic syndrome develop central nervous system problems and subsequent coma, hemiparesis, or stroke.[27,28] In one review of 49 hemolytic uremic syndrome studies, investigators found that of 3,476 patients with diarrhea-positive hemolytic uremic syndrome, 313 (9 percent) died, 104 (3 percent) developed end-stage renal disease, and 869 (25 percent) exhibited renal sequelae.[28] Neurologic involvement correlates highly with a fatal outcome.[29]

TABLE 5
Common Complications Associated with Hemolytic Uremic Syndrome

Gastrointestinal
Intestinal strictures/perforations
Intussusception
Pancreatitis
Severe colitis
Neurologic
Altered mental status
Focal neurologic signs
Seizures
Renal
Chronic renal failure
Hematuria
Hypertension
Proteinuria

Prognosis

Infection-induced hemolytic uremic syndrome presents with a diarrheal prodrome and has a good prognosis. The average length of hospital stay in children is 11 days, with a range of one to 388 days.[12] Genetic, drug-induced, or idiopathic hemolytic uremic syndrome is heterogeneous, is not preceded by diarrhea, and has a poor prognosis, with incomplete recovery in most cases. Currently, the mortality rate for all patients with hemolytic uremic syndrome is less than 10 percent.[30]

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