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In Brief

Hemolytic-Uremic Syndrome

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Hemolytic-uremic syndrome (HUS), the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency, is the leading cause of renal failure in the United States in previously healthy children, in particular those younger than 3 years of age. There are two broad etiologic categories: typical HUS (with diarrhea, or D+) and atypical HUS (without diarrhea, or D−). Some 90% of HUS in the United States is classified as D+, and most cases are caused by shiga-toxin-producing strains of *Escherichia coli* (STEC), most often the O157:H7 subtype.

Although *E coli* are part of the normal intestinal flora, the bacteria have acquired the ability to cause disease in the gastrointestinal (GI) tract. STEC, also called enterohemorrhagic *E coli*, is the only pathotype of *E coli* causing disease in children in the United States. The STEC pathotype is related closely to enteropathogenic *E coli*, the cause of traveler's diarrhea, with the acquired ability to produce shiga-like toxin. STEC most commonly infect children from 9 months to 4 years of age in the summer and fall. The primary reservoir of STEC in the United States and Western Europe is cattle.

Typical HUS is a toxin-mediated disease. The two shiga-like toxins associated with *E coli* O157:H7 are ST-1 and ST-2, which bind to cell surface receptors, translocate into the cell, interrupt protein synthesis, and ultimately cause cell death, with the resultant release of proinflammatory and prothrombotic molecules. Thrombotic microangiopathy is the classic histologic finding in HUS. In the gut, enterocyte death and disruption of the microvasculature manifest as hemorrhagic colitis. The glomerular endothelium is similarly susceptible, with cell injury leading to the intravascular creation of a fibrin meshwork that damages platelets and red blood cells.

HUS is diagnosed clinically. Children often present with abdominal pain, followed in 35% to 90% by diarrhea that becomes bloody. Fever frequently is low grade or absent, and the colitis is self-limited. During the diarrheal prodrome, antibiotics and antimotility agents should be avoided because they have shown no significant benefit and may worsen disease. HUS develops 2 to 14 days after the onset of diarrhea, with a median time to onset of 6 days. Approximately 10% to 15% of children infected with *E coli* O157:H7 develop HUS, and 40% to 50% of children afflicted with typical HUS eventually develop oligoanuric renal failure, requiring dialysis. Therefore, monitoring volume status in affected children is essential. Decreasing urine output or increasing edema in a child who has a history of bloody diarrhea and appears well-hydrated should prompt inclusion of HUS in the differential diagnosis. Children may become pale and develop icterus from hemolysis and become hypertensive, both from volume overload and activation of the renin-angiotensin system by ischemic kidneys. Children who have hypertension have a poorer prognosis. Thrombocytopenia may produce petechiae, but this usually does not lead to significant bleeding. Central nervous system (CNS) involvement occurs in 15% to 20% of children who have HUS, most commonly as seizure or coma.

Laboratory findings in HUS include microangiopathic hemolytic anemia, with a hemoglobin level of less than 10 g/dL (100 g/L) and a negative direct antiglobulin (Coombs) test. Schistocytes and helmet cells, reflecting mechanical trauma within vessels, may appear on the smear. Typical findings accompanying hemolysis include increased indirect bilirubin, decreased haptoglobin, and increased lactate dehydrogenase values. Thrombocytopenia

usually is about 40×10^3/mcL (40×10^9/L). Prothrombin time and partial thromboplastin time are normal. Urinalysis shows hematuria and proteinuria. Blood urea nitrogen (BUN) and creatinine concentrations are elevated, and the albumin concentration may be decreased from protein loss in the GI tract.

A complete blood count with smear as well as BUN and creatinine measurements should be obtained in all children who have a history of bloody diarrhea (whether gross or occult). Additionally, the stool of patients who have HUS and their contacts who have developed diarrhea should be cultured specifically for *E coli* O157:H7 by using MacConkey agar plates because this subtype does not ferment sorbitol. Clinicians should be aware of the methods used by their local microbiology laboratories to identify STEC. A negative stool culture in a patient who has HUS does not eliminate STEC as the cause; isolation in the stool is most successful in the 6 days following the onset of diarrhea.

Treatment for D+HUS generally is supportive. Careful monitoring of volume status, paying particular attention to urine output and daily weight, is integral. Early volume expansion and maintenance fluid therapy with isotonic fluid may decrease the risk of progression to oligoanuric renal failure. Volume expansion in a child who has HUS is a delicate balancing act. In the child who has euvolemia and oliguria, fluid administration should be restricted to insensible losses plus urine output. Dialysis is indicated for patients whose BUNs are greater than 80 to 100 mg/dL (28.6 to 35.7 mmol/L), for fluid overload that is not responsive to diuretic therapy, or for electrolyte abnormalities such as hyperkalemia and acidosis. Transfusion of packed red blood cells is indicated for hematocrit levels below 15% to 18% (0.15 to 0.18). Platelet transfusions should be avoided, except in cases of active bleeding or when an invasive procedure is required. The use of antibiotics in HUS is controversial; most physicians agree that they should be avoided in the treatment of *E coli* O157:H7 infection until additional studies are performed to evaluate the associated risks and benefits.

Risk factors for the development of HUS in children who have diarrhea include blood in the stool, leukocytosis, and administration of antimotility agents. The risk of developing HUS is lower if no hemolysis, thrombocytopenia, or CNS involvement is present 3 days after the resolution of diarrhea. Factors associated with a more severe course of HUS and with subsequent long-term renal problems include anuria lasting for more than 2 weeks or occurring early in the course of illness, a neutrophil count greater than 20×10^3/mcL (20×10^9/L), coma, atypical disease, renal cortical necrosis, thrombi in more than 60% of glomeruli, extraglomerular renal involvement, severe diarrheal prodrome, and age younger than 2 years.

Acute mortality in HUS is 3% to 5%, mostly from CNS involvement, cardiac failure, or multiorgan failure. Long-term studies have shown that 50% to 70% of patients recover normal renal function; 5% suffer severe and permanent renal or CNS sequelae. The remainder demonstrates a variable combination of persistent proteinuria, hypertension, and diminished glomerular filtration rate, and 10% of this group eventually develops end-stage renal disease. Thus, meticulous follow-up is crucial, and children who have had HUS need yearly evaluation, including measurement of blood pressure and serum creatinine as well as urinalysis. For patients who have typical disease and eventually require kidney transplantation, recurrence in the graft is rare.

Because there is no cure for HUS and because a significant proportion of affected children develop renal sequelae, prevention and infection control are key areas of focus for the pediatric practitioner, along with patient education. To prevent the spread of *E coli* infection, ground beef should be cooked thoroughly. Unpasteurized milk and juices should be avoided because outbreaks have been linked to these food products. The impact of good hand hygiene, in both food preparation and contact with patients, cannot be overestimated. Contact precautions should be implemented for any child who has bloody diarrhea until the diarrhea resolves and two stool cultures are negative. An infected child should not be allowed to return to group child care (also a common link to outbreaks of infection) until the aforementioned criteria are met. *E coli* O157:H7 colitis in child care centers should be reported to local public health authorities. Additionally, attendees should not be allowed to transfer to other centers until the outbreak has been controlled.

Comment: In years past, HUS was believed to be the pediatric relative of a clinically similar syndrome seen more commonly in adults—thrombotic thrombocytopenic purpura (TTP). Recent investigations have revealed that they are distinct in their underlying causes. Whereas typical HUS is a toxin-mediated disease, TTP results from a deficiency in ADAMTS-13, a metalloprotease that cleaves von Willebrand Factor (vWF). In familial TTP, the deficiency is inherited; in acquired disease, autoantibodies against the enzyme produce a functional deficiency. Without the action of ADAMTS-13, ultra-large multimers of vWF accumulate, leading to abnormal platelet aggregation in the microvasculature and, thus, to thrombosis, thrombocytopenia, and neurologic and renal damage that characterizes TTP. Of historical interest, although TTP typically is a disease of adults, the first reported case in the 1920s was in a 16-year-old patient.

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Editor, In Brief

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