Hemolytic–Uremic Syndrome

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Objectives   After completing this article, readers should be able to:

1. Describe the laboratory findings in hemolytic–uremic syndrome (HUS).
2. Delineate the signs and symptoms of HUS.
3. Characterize the association between verotoxin-secreting *Escherichia coli* and HUS.
4. Outline the prognostic factors in HUS.
5. Describe appropriate initial and long-term management of a child who has HUS.

Introduction

The hemolytic-uremic syndrome (HUS) has been recognized for more than 45 years and consists of the combination of hemolytic anemia, thrombocytopenia, and acute renal failure. HUS occurs predominantly in children younger than 4 years of age. It is the most frequent cause of acute renal failure in children. The most common form of the syndrome (D+ HUS) occurs in healthy young children (>6 mo to <5 y of age) and is preceded by watery diarrhea that can evolve to hemorrhagic colitis. The diarrhea precedes the hemolysis and thrombocytopenia by 5 to 7 days; oliguria/anuria follows several days later. Although the pathogenesis is unknown, available evidence strongly suggests that endothelial cell damage is necessary. The outcome for most patients who have D+ HUS is favorable: 65% to 85% recover completely, 5% to 10% die (usually during the acute illness), recurrence is uncommon, and only a few patients slowly progress to end-stage renal disease (ESRD).

Definitions

HUS is defined as the combination of a microangiopathic hemolytic anemia with variable degrees of thrombocytopenia and renal failure. The syndrome usually occurs in previously healthy children and often is preceded by a gastrointestinal enteritis. Other systems may be involved, such as the central nervous system (CNS). When fever and CNS manifestations coexist, the distinction between HUS and thrombotic thrombocytopenic purpura (TTP) can be difficult.

Epidemiology

HUS has been characterized as either epidemic/endemic (or prodromal) or sporadic (nonprodromal). The epidemic type is more common and is accompanied by an enteritis prodrome (D+ HUS); the sporadic type is not accompanied by enteritis (D− HUS). The etiology and prognosis differ between the D+ and D− types (Table 1). The etiology of D+ HUS has been strongly linked to a toxin-producing strain of *Escherichia coli* (0157: H7). Race and gender are not predisposing factors. A number of other microorganisms have been implicated in the pathogenesis of postdiarrheal HUS, especially enterohemorrhagic *E coli* and, in some areas, *Shigella dysenteriae* type 1. These infectious agents are acquired by the consumption of raw or undercooked ground beef, unpasteurized milk, and contaminated water or apple juice and by person-to-person contact.

The sporadic form of HUS (also called atypical HUS) is rare in childhood. This type has a worse prognosis, is more likely to relapse, has no preceding diarrhea, and may be associated with a family history of HUS disease. It appears to be associated with certain

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Table 1. ## Features of Typical (D+ HUS) and Atypical (D− HUS) Hemolytic–Uremic Syndrome

Feature	D+ HUS	D− HUS
Pathogenesis	Shiga-like toxin, usually associated with *Escherichia coli* (0157:H7)	*Streptococcus pneumoniae* infection Drugs (eg, cyclosporine, tacrolimus) Primary glomerulopathies Familial collagan/vascular disorders
Prodrome	Watery, then bloody diarrhea	None or respiratory
Age at onset	Similar	Similar
Morbidity	Low (~5%)	High (~25%)
End-stage renal disease	Uncommon (~10%)	Common (~30%)
Recurrences	Uncommon	Common (~50%)
Treatment	Supportive, dialysis	Supportive, dialysis, ± plasmapheresis

chemotherapy drugs, oral contraceptives, cancer, bone marrow transplantation, and vasculitic diseases. This article concentrates on the more common D+ HUS type of disease

Pathogenesis

D+ HUS is associated with an infection with verocytotoxin (VT)- or Shiga-like toxin-producing *E coli* 0157:H7, *Shigella dysenteriae* type 1, *E coli* 026:H11, and other infectious agents. At least three different toxins are designated as VT-1, VT-2, and VT-2c. The toxin binds, invades, and destroys colonic mucosal epithelial cells, resulting in bloody diarrhea. After entering the systemic circulation, the toxin attaches to a membrane glycosphingolipid receptor (globotriaosylceramide) on endothelial cells (especially in the kidney). The endothelial cells swell and are injured. In the process, certain endothelial products are released (eg, von Willebrand factor, platelet aggregating factor, plasminogen activator inhibitor-1), and platelet/fibrin thrombi form in these injured areas. In addition to the kidney, the pancreas, brain, and other organs may be injured.

The circulating red blood cells that are forced through these occluded vessels are deformed and fragment, which produces the characteristic schistocytes (Figure). These fragmented red cells are removed by the reticuloendothelial system, resulting in hemolytic anemia (thus, the term micoangiopathic hemolytic anemia). Because platelets are consumed in the process of vascular injury, most patients also develop some degree of thrombocytopenia.

Clinical Picture

The clinical picture of HUS is a previously healthy child who develops abdominal pain and diarrhea, followed shortly thereafter by bloody diarrhea. There may be fever. Within 5 to 7 days, the patient exhibits signs of anemia (eg, pallor with or without jaundice) and thrombocytopenia (eg, petechiae). Other signs may include hepatomegaly, hypertension, oliguria, and CNS (eg, drowsiness, personality changes) and more severe gastrointestinal manifestations, such as intussusception or gangrenous bowel. Splenomegaly is not a consistent finding, and bleeding (other than the bloody diarrhea) is rare. Within a few days, anuria occurs. At this point, other clinical manifestations may appear, such as coma, hemiparesis, cranial nerve dysfunction, cerebral infarcts, seizures, pancreatic insufficiency, and death.

Hematologic Aspects

The anemia is characterized as normochromic-normocytic with an elevated reticulocyte count. The blood smear reveals fragmented cells (helmet cells or
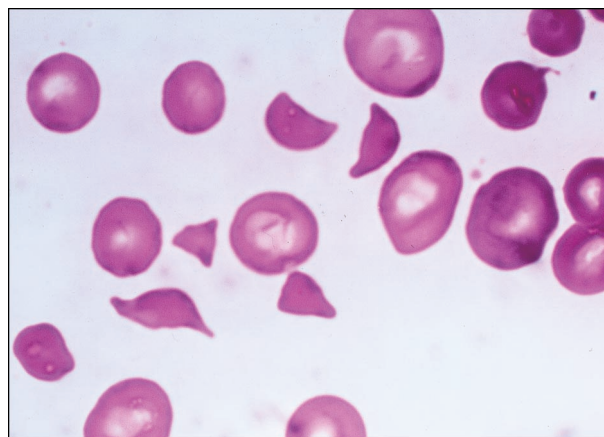

Figure. Blood smear (Wright stain) from a patient who has HUS. Note schistocytes (red blood cell fragmentation) and reduced number of platelets.

schistocytes) and polychromatophilia. The median hemoglobin count is 8 g/dL (80 g/L), and the hematocrit is 24% (0.24). Results of the direct antiglobulin test are negative. The serum haptoglobin concentration is low, and the lactate dehydrogenase level is elevated. Unconjugated hyperbilirubinemia is usually noted. The degree of the anemia is not related to the acute renal failure. The platelet count is moderately reduced at approximately 50×10^3/mcL $(50 \times 10^9$/L), but it can be as low as 5×10^3/mcL $(5 \times 10^9$/L). At the onset, approximately 50% of patients have counts greater than 100×10^3/mcL $(100 \times 10^9$/L). Neither the severity nor the duration of thrombocytopenia correlates with overall severity of disease. The thrombocytopenia lasts for 7 to 20 days. However, platelet function abnormalities persist for several weeks. The changes in the white blood cell count and white blood cells themselves are nonspecific and, therefore, not helpful diagnostically. Coagulation test results are uniformly normal, including prothrombin time, partial thromboplasin time, and fibrinogen levels. A test for fibrin split/degradation products may yield positive results. Some reports have noted increased plasma levels of tissue-type plasminogen activator and plasminogen activator inhibitor-1, but the significance of these findings is unclear. Bone marrow examination in these patients shows only erythroid hyperplasia and normal megakaryocytes.

Table 2 displays those conditions associated with red blood cell fragmentation hemolytic anemia. HUS and TTP occur in previously healthy children and are accompanied by thrombocytopenia. Unless there are significant CNS signs, the diagnosis of HUS should be clear.

Renal Aspects

Renal involvement in HUS can vary from mild to severe. Children in whom the renal involvement is mild have only microscopic hematuria, minimal proteinuria, and normal urine output. Some may have an increased urine volume. Severe involvement is characterized by anuria, widespread renal cortical necrosis, and irreversible anuric renal failure. Most affected children have features between these two extremes. The majority of patients (60%) experience oliguria that lasts an average of 1 week. Almost 50% are anuric for an average of 3 days. If there is oligoanuria, it can continue for weeks. All patients have hematuria and proteinuria unless anuric. Red blood cell casts frequently are found if carefully sought.

Renal dysfunction is indicated by elevated serum levels of creatinine and blood urea nitrogen (BUN). A variety of fluid and electrolyte imbalances occur because of reduced renal function, hemolysis, and tissue catabo-

Table 2. Red Blood Cell Fragmentation Conditions (Schistocytes)

- Hemolytic–uremic syndrome
- Thrombotic thrombocytopenia purpura
- Disseminated intravascular coagulation
- Preeclampsia/eclampsia
- Systemic lupus erythematosus
- Artificial cardiac valves
- Intracardiac patches
- Hemolytic transfusion reaction

lism. These include hyponatremia that is usually dilutional; hyperkalemia from reduced glomerular filtration rate, hemolysis, and tissue catabolism; metabolic acidosis from reduced renal function and tissue catabolism; and hyperphosphateria and hypocalcemia. Fluid overload is common and can lead to edema and cardiac failure.

Hypertension is a common feature of HUS. It occurs at some point in the illness in almost 50% of children and can be severe. The etiology of hypertension often is obscure. Studies have reported both increased and normal renin activity. Volume overload caused by reduced renal function with fluid retention is another potential cause of hypertension.

Renal biopsy rarely is needed in children who have the characteristic clinical and laboratory features of HUS. It may be helpful following resolution of the acute phase of the illness to determine the degree of chronic injury and, therefore, long-term prognosis.

Other Aspects

Although the gastrointestinal, renal, and hematologic systems are affected most commonly in HUS, injury to other systems also can be clinically important. CNS involvement is evident in 20% to 30% of patients, with seizures being the most commonly reported observation in 3% to 5% of the cases. Pancreatic insufficiency occurs in 4% to 15% of patients and is manifested as diabetes mellitus, which usually is transient. The liver, heart (myocarditis, cardiomyopathy), and muscle also can be involved.

Management

The management of patients who have D+ HUS is primarily supportive and designed to reverse the renal failure and to control hypertension (when it exists). Red

blood cells are infused for symptomatic anemia. Platelet transfusions rarely are administered because a generalized bleeding diathesis is not common, and theoretically platelet infusions could contribute to the microthrombosis. However, platelet transfusion may be indicated prior to surgical procedures, such as catheter placement for hemodialysis or peritoneal dialysis. Other therapies, including antiplatelet drugs, intravenous immune globulin, anticoagulants, thrombolytic agents, prostacyclin, and corticosteroids, have not been found to be beneficial. Although plasma infusion or plasma exchange has been found to be beneficial in TTP, results in patients who have HUS have not been convincing. A recent report suggests that the risk of developing HUS is increased after antibiotic therapy for *E coli* 0157:H7 enteritis. This observation has not been confirmed.

The principles of managing fluid and electrolyte imbalances in D+ HUS and D− HUS are similar. Imbalances must be corrected and the fluid and electrolyte status of each patient monitored constantly. Nutrition support to achieve normal caloric intake is very important and can be administered intravenously, orally, or by tube feeding. Gastrointestinal feeding is performed as long as it does not cause undue pain or increased diarrhea and the integrity of the gastrointestinal tract is not compromised. Peritoneal dialysis or hemodialysis should be considered when fluid and electrolyte imbalances cannot be corrected by replacement fluids or when fluid overload compromises cardiac or pulmonary function. Optimal nutrition support often requires intravenous infusion or oral administration of large volumes of fluid, which may necessitate dialysis. Multiple or large-volume transfusion of packed red blood cells may lead to pulmonary edema and congestive heart failure, with dialysis required to remove excess plasma volume during the transfusion. As a general principle, when the BUN exceeds 100 mg/dL (35.7 mmol/L), dialysis should be considered even in the absence of fluid and electrolyte imbalances.

Hypertension should be treated to prevent encephalopathy and congestive heart failure. Short-acting calcium channel blockers, such as nifedipine, can be administered orally. If oral administration is not possible, intravenous administration of nicardipine or nitroprusside should be considered. Intravenous nicardipine or nitroprusside also is indicated if there is evidence of hypertensive encephalopathy.

Plasmapheresis may be of benefit in the atypical form of HUS (D− HUS), especially when symptoms of neurologic involvement are present. The effect of plasmapheresis on renal involvement is less encouraging in D− HUS.

Prognosis

The major improvement in prognosis for HUS has resulted from careful management of fluid and electrolytes and early initiation of dialysis to correct fluid overload or severe electrolyte imbalances. The overall prognosis for D+ HUS is better than for D− HUS. The early mortality rate is about 5%. Another 5% of patients develop acute renal failure and anuria, requiring lifelong dialysis. The long-term prognosis is more problematic. Long-term complications include proteinuria, reduced glomerular filtration rate, hypertension, and late development of ESRD. Many patients in long-term studies experienced initial complete recovery, but developed complications years later. ESRD develops in approximately 10% to 15% of patients in 15- to 25-year follow-up studies. Accordingly, children who have D+ HUS should be followed for many years, even if the recovery initially appears complete. Long-term prognosis can be predicted by renal biopsy performed during the initial illness. Children who have patchy renal cortical necrosis are more likely to develop ESRD or chronic renal failure.

The prognosis of D− HUS is generally accepted to be worse than that of D+ HUS. The early mortality rate, incidence of ESRD, and frequency of chronic renal failure and hypertension are all higher in this group. Children who have D− HUS also have a higher rate of recurrence; recurrences are infrequent among those who have D+ HUS. Recurrences of HUS after renal transplantation are much more common with D− HUS than D+ HUS.

Suggested Reading

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PIR Quiz

Quiz also available online at *www.pedsinreview.org.*

1. You are considering the diagnosis of hemolytic–uremic syndrome (HUS) in a 3-year-old child who has bloody diarrhea and a blood urea nitrogen concentration of 65 mg/dL (23.2 mmol/L). In reviewing the peripheral blood smear, which of the following types of blood cells would be *most* consistent with the diagnosis?

   A. Atypical lymphocytes.
   B. Eliptocytes.
   C. Myeloblasts.
   D. Schistocytes.
   E. Spherocytes.

2. In HUS, any prodromal bloody diarrhea is *most* likely caused by:

   A. *Clostridium difficile* infection.
   B. Intussusception.
   C. Stress ulcer.
   D. Thrombocytopenia.
   E. Verocytotoxin.

3. In the management of a 2-year-old child who has HUS, which of the following clinical findings is the *strongest* indication for dialysis?

   A. Blood urea nitrogen level of 110 mg/dL (39.3 mmol/L).
   B. Heart rate of 140 beats/min for 24 hours.
   C. QT$_c$ of 0.425.
   D. Serum sodium concentration of 155 mEq/L (155 mmol/L).
   E. Urine output of <150 mL/d for 2 days.

4. The *best* indicator of a good long-term prognosis in a patient who has HUS is:

   A. Being symptom–free 6 months after the initial illness.
   B. Having biopsy evidence of patchy renal cortical necrosis.
   C. Having the epidemic type.
   D. Not experiencing prodromal diarrhea.
   E. Undergoing renal transplantation.