The hemolytic-uremic syndrome (HUS) is the most common cause of acute renal failure in young children.

It is classically characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and uremia.

**ETIOLOGY.**

An acute enteritis with diarrhea caused by Shiga-like toxin–producing *Escherichia coli* 0157: H7 precedes 80% or more of HUS cases in developed countries.

The reservoir of this organism is the intestinal tract of domestic animals. It is usually transmitted by undercooked meat or unpasteurized milk. Outbreaks have usually followed ingestion of undercooked hamburger at fast food restaurants. Outbreaks also occur with diarrheal epidemics after swimming in contaminated ponds, lakes, or pools as well as eating contaminated milk, cheese, lettuce, or apple cider.

The organism produces a Shiga-like verotoxin that is absorbed from the intestines and initiates endothelial cell injury.

HUS is also associated with *Shigella* and less commonly with other bacterial (*Salmonella, Campylobacter, Streptococcus pneumoniae, Bartonella*) and viral (*coxsackievirus, echovirus, influenza, varicella, HIV, Epstein-Barr*) infections. HUS may also develop with the use of oral contraceptives, mitomycin, or cyclosporine.

Several reports describe its occurrence in more than one member of a family. Familial occurrences are usually not associated with diarrhea and may be autosomal recessive or dominant disorders. Mutations in complement component H (inhibits activation of the alternate complement pathway) are noted in 10–20% of familial cases. Complete deficiency of the von Willebrand factor metalloprotease (cleaves multimers of von Willebrand factor) and of membrane cofactor protein is responsible for other familial cases.

**PATHOGENESIS.**

The primary event in the pathogenesis of the syndrome is endothelial cell injury. Capillary and arteriolar endothelial injury in the kidney leads to localized clotting. Evidence of disseminated intravascular coagulation is unusual. Microangiopathic anemia results from mechanical damage to red blood cells (RBCs) as they pass through the altered vasculature. Thrombocytopenia is caused by intrarenal and diffuse microvascular platelet adhesion or damage. Damaged RBCs and platelets are removed from circulation
by the liver and spleen. Nondiarrheal and sporadic recurrent familial cases of HUS are associated with low complement (C3) levels due to complement dysregulation and activation following an inciting injury to the endothelial cell.

**CLINICAL MANIFESTATIONS.**

**HUS is most common in children younger than 4 yr of age.** The onset is usually preceded by a gastroenteritis characterized by fever, vomiting, abdominal pain, and diarrhea that is initially watery but then becomes bloody.

Less commonly, patients may present after an upper respiratory tract infection.

Sudden onset of pallor, irritability, weakness, lethargy, and oliguria usually occurs 5–10 days after the initial gastrointestinal or respiratory illness. Physical examination may reveal dehydration, edema, petechiae, hepatosplenomegaly, and marked irritability.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS.**

The diagnosis is supported by the findings of a microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure.

- The hemoglobin value is commonly in the 5–9 g/dL range.

- The blood peripheral smear reveals helmet cells, burr cells, and fragmented RBCs.

- The reticulocyte count is moderately elevated, and the Coombs test result is negative.

- Leukocytosis is significant, and commonly the leukocyte count may exceed 30,000/mm³. Thrombocytopenia (20,000–100,000/mm³) occurs in more than 90% of patients.

- Findings on urinalysis are surprisingly mild and usually consist of low-grade microscopic hematuria and proteinuria.

- Partial thromboplastin time and prothrombin time are usually normal.

- Renal manifestations vary from mild renal insufficiency to acute oliguric or anuric renal failure requiring dialysis.
Definition of Postdiarrheal Hemolytic Uremic Syndrome:

CLINICAL DESCRIPTION

Hemolytic uremic syndrome (HUS) is characterized by the acute onset of microangiopathic hemolytic anemia, renal injury, and a low platelet count. Most cases of HUS occur after an acute gastrointestinal illness (usually diarrheal).

LABORATORY CRITERIA FOR DIAGNOSIS

The following are both present at some time during the illness:

- Anemia (acute onset) with microangiopathic changes (i.e., schistocytes, burr cells, or helmet cells) on peripheral blood smear; and
- Renal injury (acute onset) evidenced by either hematuria, proteinuria, or elevated creatinine level (i.e., ≥1.0 mg/dL in a child younger than 13 yr or ≥1.5 mg/dL in a person 13 yr or older or ≥50% increase over baseline).

Note: A low platelet count can usually, but not always, be detected early in the illness, but it may then become normal or even high. If a platelet count obtained within 7 days after onset of the acute gastrointestinal illness is not <150,000/mm³, other diagnoses should be considered.

<table>
<thead>
<tr>
<th>TABLE 518-2 -- Classification of Hemolytic Uremic Syndrome (HUS)</th>
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<tbody>
<tr>
<td><strong>TYPE OF HUS</strong></td>
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<td>----------------------------</td>
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<tr>
<td><strong>TYPICAL (POSTDIARRHEAL) HUS</strong></td>
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<tr>
<td>Post gastrointestinal infection</td>
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<tr>
<td><strong>ATYPICAL HUS</strong></td>
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<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Post infectious</td>
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<tr>
<td>Familial (autosomal dominant or recessive)</td>
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<td>Associated with drug use</td>
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HUS should always be considered in the child with a sudden onset of acute renal failure. The typical history, clinical picture, and laboratory findings confirm the diagnosis in most patients. A renal biopsy is rarely indicated.

**COMPLICATIONS.**

Complications include anemia, acidosis, hyperkalemia, fluid overload, heart failure, hypertension, and uremia.

Extra renal manifestations of the central nervous system, gastrointestinal tract, heart, and skeletal muscles may be life-threatening.

Central nervous system dysfunction includes irritability, seizures, infarcts of the basal ganglion and cerebral cortex, cortical blindness, and coma.

Gastrointestinal manifestations include ischemic or inflammatory colitis, intestinal perforation, intussusception, and hepatitis.

Focal pancreatic necrosis may result in acute pancreatitis, glucose intolerance, insulin-dependent diabetes mellitus, and elevated lipase levels.

Pericarditis, myocardial dysfunction, and arrhythmias may be seen in cases with cardiac involvement. Other complications such as skin necrosis, parotitis, adrenal dysfunction, and rhabdomyolysis have been reported.

**PROGNOSIS AND TREATMENT.**

Supportive care with meticulous attention to fluid and electrolytes, control of hypertension, aggressive nutrition, and early institution of dialysis has been responsible for a decrease in the mortality from this disease from 80% to less than 10% over the past 30 yr.

**Antibiotics should be avoided in patients with acute enteritis presumed secondary to* E. coli* 0157: H7 as they may increase the risk of developing HUS.**

Nephroprotection in the early phase of HUS may be possible by prevention of dehydration with intravenous fluids.

Peritoneal dialysis controls fluid and electrolyte abnormalities, maintains a normal intravascular volume, and provides the opportunity for aggressive nutritional support.

With aggressive management of acute renal failure, more than 90% of patients survive the acute phase of HUS with a diarrheal prodrome.
Death or end-stage renal disease affects 12%. Hypertension, proteinuria, or low glomerular filtration rates (<80 mL/min/1.73 m²) affects 25%.

The overall prognosis of HUS is associated with negative long-term renal outcomes when central nervous symptoms (coma, stroke, seizures) are present during the acute illness and dialysis is required. Other predictive factors for acute or chronic severity include a white blood cell count >20,000, ischemic colitis, and hypertension.

Patients recovering from the acute phase of HUS require long-term follow-up because complications such as hypertension, chronic renal insufficiency, and proteinuria may not be apparent for up to 20 yr.

Kidney transplantations in patients with HUS can be successful, although there may be disease recurrence, particularly in familial or non–diarrhea-associated cases.

Combined liver and renal transplantation may be an option for those familial cases associated with compliment factor H mutations.