An Overview of Pediatric Hemolytic Uremic Syndrome

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EDUCATION GAP

Hemolytic uremic syndrome (HUS) is one of the main causes of community-acquired acute kidney injury (AKI). AKI is responsible for significant morbidity and mortality in the pediatric population. Pediatricians must understand the new nomenclature of HUS as well as recognize the different signs and symptoms of this entity to initiate prompt treatment.

OBJECTIVES *After completing this article, readers should be able to*

1. Identify the signs and symptoms of HUS.
2. Discuss the initial evaluation and management of suspected HUS.
3. Describe the updated terminology for classifying HUS.
4. Make pertinent subspecialty referrals to support patients with HUS.
5. Discuss the prognosis of HUS.

CASE

A previously healthy 4-year-old girl with incomplete vaccinations presented for an evaluation of 5 days of fever (T-max 39 °C), severe cough, increased work breathing, and chest and back pain. Laboratory analysis revealed a white blood cell count of 10.4 10K/μL, anemia with a hemoglobin of 9.2 g/dL, thrombocytopenia with a platelet count of 12 610 K/μL, C-reactive protein of 38.9 mg/dL, and procalcitonin of 440 ng/mL. Coagulation studies were abnormal, with a prothrombin time (PT) of 19.3 seconds (nl 11.6–15.4 seconds), partial thromboplastin time (PTT) of 65.3 seconds (nl 22.8–38.2 seconds), and fibrinogen of 1055 mg/dL. Renal function was normal. A chest radiograph demonstrated a near-complete whiteout of the right hemithorax with a pleural effusion. Such findings were confirmed by an ultrasound and computed tomography scan, which showed necrotizing pneumonia with a significantly large complex pleural effusion. A blood culture was obtained, and the patient was started on broad-spectrum antibiotics for pneumonia. Soon after admission, the patient decompensated with worsening respiratory distress, decreased urine output with a 3-L positive fluid balance, and hypertension. Repeat laboratory studies showed worsening anemia with a hemoglobin of 8.7 g/dL and worsening thrombocytopenia with a platelet count of 2110 K/μL. Additional tests to check for hemolysis demonstrated a lactate dehydrogenase (LDH) of 5589 IU/L, uric acid

AUTHOR DISCLOSURE: Drs Fraustro and Clemente have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AKI	acute kidney injury
C3	complement 3
C4	complement 4
CFB	complement factor B
CFI	complement factor I
CHF	complement factor H
DAT	direct antiglobulin test
DGKε	diacylglycerol kinase ε
DIC	disseminated intravascular coagulation
GB3	globotriaosylceramide-3
HUS	hemolytic uremic syndrome
LDH	lactate dehydrogenase
MAC	membrane attack complex
MAHA	microangiopathic hemolytic anemia
MCP	membrane-cofactor protein
PT	prothrombin time
PTT	partial thromboplastin time
SC5b-9	soluble terminal complement complex enzyme
S. pneumoniae	*Streptococcus pneumoniae*
STEC	Shiga toxin–producing *Escherichia coli*
TF antigen	Thomsen-Friedenreich
TMA	thrombotic microangiopathy antigen
TTP	thrombotic thrombocytopenic purpura
US	ultrasound
WBC	white blood cell count

of 6.3 mg/dL, haptoglobin of <20 mg/dL, a Coombs-positive result, and the presence of schistocytes identified on a blood smear. The patient also developed intrarenal acute kidney injury (AKI) with a creatinine of 1.37 mg/dL and blood urea nitrogen of 62 mg/dL and required hemodialysis. The patient was in multiorgan failure; she was intubated and started on mechanical respiratory support. A chest tube was placed, and pleural fluid cultures were positive for *Streptococcus pneumoniae*. Stool culture was negative for Shiga toxin–producing *Escherichia coli* (STEC). Further studies showed low complement levels: C3 level of 49.2 mg/dL (92–184 mg/dL), C4 level of 4.5 mg/dL (20–59 mg/dL), elevated soluble terminal complement complex enzyme (SC5b-9) of 1415 ng/mL (normal <244 ng/mL), and normal "a thrombospondin type 1 motif, member 13" (ADAMTS13) activity of 38%. These findings were consistent with HUS secondary to *S. pneumoniae*. The patient received 4 doses of eculizumab with a good response; she completed antibiotic treatment, did not develop significant sequelae, and was later discharged.

INTRODUCTION

Thrombotic microangiopathies (TMAs) are a group of disorders characterized by injury and occlusion of microvessels that arise from an endothelial injury, resulting in tissue ischemia and end-organ damage. The TMA umbrella includes but is not limited to HUS, thrombotic thrombocytopenic purpura (TTP), and disseminated intravascular coagulopathy (DIC). Given the overlap between presentations, TMAs represent a diagnostic and therapeutic challenge for clinicians.[1] Due to the critical nature of acute TMAs, a significant proportion of affected patients require admission to the intensive care unit upon presentation, many of whom are not diagnosed at the time of admission. A thorough clinical and laboratory evaluation is essential to arrive at an accurate diagnosis, which is key for appropriate management. HUS is a TMA that mainly affects the kidneys and is the most common cause of TMA in young children.[2] HUS is classically defined by the triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and AKI. HUS can be primary or secondary, both of which vary widely in severity and treatment. This article outlines the current nomenclature for HUS as well as the initial diagnostic evaluation and management of HUS, particularly of primary HUS, STEC-HUS, and *S. pneumoniae* HUS.

DEFINITIONS AND CLASSIFICATION

Historically, HUS was classified as "diarrhea positive" (typical) and "diarrhea negative" (atypical). STEC-HUS was referred to as typical HUS. All other causes of HUS were referred to as atypical HUS. Often, children with atypical HUS had persistent or recurrent disease, and some had a family history of HUS. These observations contributed to significant advances in the understanding of the etiology and pathophysiology of HUS, particularly the role of the alternative complement pathway. The terminology for HUS is constantly evolving as our understanding of its pathophysiology improves (Figure 1). HUS should be referred to as primary or secondary HUS based on the pathophysiology. Primary HUS, formerly referred to as atypical, is a disorder of complement regulation due to an underlying genetic predisposition. Secondary HUS, formerly referred to as typical, is caused by an internal or external event (infection, malignancy, transplantation, drugs, autoimmune disease).

TTP is a primary TMA syndrome caused by a severe reduction in the function of the von Willebrand factor–cleaving protease ADAMTS13, which promotes the formation of platelet microthrombi. TTP is classically described by the following pentad: MAHA, thrombocytopenia, fever, neurologic symptoms, and AKI. Among the primary TMA syndromes, TTP is remarkable for causing minimal kidney function abnormalities.

DIC is an acquired systemic syndrome of the coagulation system resulting in consumptive coagulopathy, leading to hemorrhage and pathologic thrombosis.

EPIDEMIOLOGY

Most pediatric HUS cases worldwide are due to a STEC infection (Figure 2). A total 90% of HUS cases are related to Shiga toxin–producing bacteria (*E. coli*, *Shigella dysenteriae*), 5% of cases are attributed to *S. pneumoniae* or other secondary causes, and primary HUS accounts for 5% of cases. STEC-HUS is a disease of children mainly aged younger than 5 years; the incidence peaks during summer and fall and varies depending on geographic location.[3] In North America and Europe, the annual incidence is 1.9 to 2.9 cases per 100 000 children aged 3 to 5 years. However, the incidence of STEC-HUS in Latin America is 10 times higher.[4] Of the patients with sporadic STEC gastroenteritis, 5% to 10% develop HUS; however, that frequency can reach up to 20% during outbreaks.

Primary HUS is a rare disorder; the annual incidence is estimated to be 0.23 to 0.42 cases per million.[5]

PATHOGENESIS

The hallmark of HUS is a procoagulant and proinflammatory state of activated endothelial cells and an overactivation of the complement cascade.

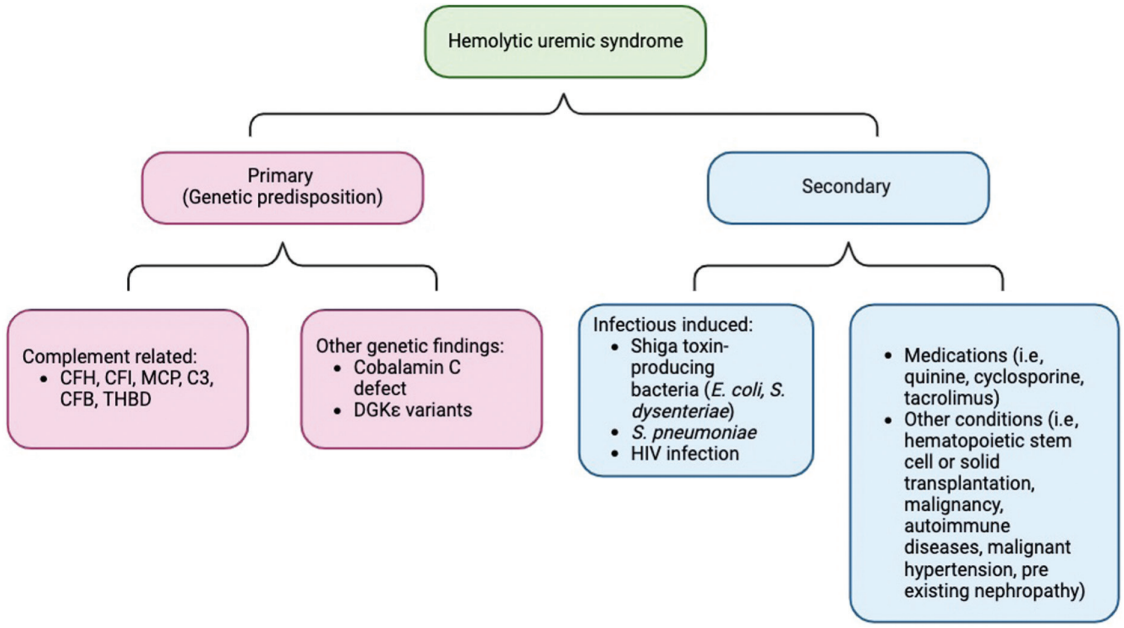

FIGURE 1. Classification of HUS. C3, component 3; CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; DGKε, diacylglycerol kinase ε; MCP, membrane cofactor protein; THBD, thrombomodulin.

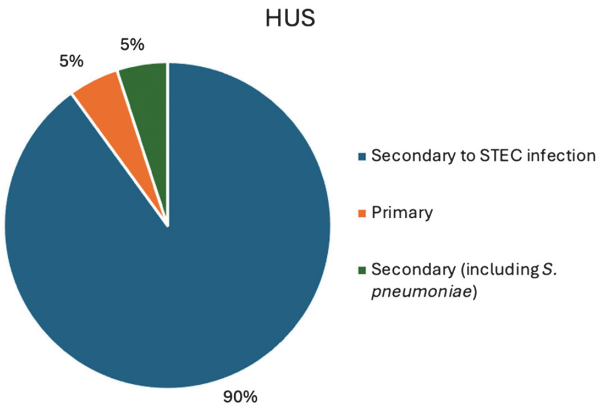

FIGURE 2. HUS epidemiology. HUS, hemolytic uremic syndrome; STEC, Shiga toxin–producing *Escherichia coli*

Complement is part of the innate immune response, assisting host cells in eliminating pathogens through 3 distinct pathways: classical, lectin, and alternative. These pathways converge to produce C3 convertase, a complex that initiates the formation of the C5-9 membrane attack complex (MAC) to destroy target cells by adhesion and lysis.[6] Activation of the MAC causes endothelial cell swelling and microvascular thrombosis, particularly in the kidneys and, to a lesser extent, other organs. The endothelial damage results in hemolysis, which can lead to further complement activation, endothelial injury, platelet aggregation, and microthrombi, which in turn causes further hemolysis that can lead to further complement activation, initiating a vicious cycle.[7] Hemolysis is due to intravascular red blood cell fragmentation. Complement activation can be initially triggered by any stress on the body, such as an infection, surgery, or inflammation.

Primary HUS

Primary HUS is a disorder of complement regulation due to an underlying genetic predisposition. In healthy conditions, the complement alternative pathway is constantly "on" but tightly controlled. However, in primary HUS, the complement alternative pathway is inappropriately activated through gain-of-function mutations (CFB or C3) or is uninhibited via loss-of-function mutations (CFH, CFI, MCP, THBD) of complement regulators or via autoantibodies to CFH.[1] The initial activation of complement is usually triggered by stress to the body. Overactivation of complement can be sustained or relapsing, leading to poor outcomes.

There are other rare genetic conditions that lead to permanent endothelial cell activation, such as coagulation disorders, DKGε mutations, metabolism defects, and cobalamin C deficiency.[7]

Secondary HUS

Secondary HUS is caused by an internal or external event, such as infections (STEC, *S. dysenteriae*, *S. pneumoniae*, influenza virus infections), cancer, transplantation, autoimmunity, or drugs. In these scenarios, once the trigger is removed or controlled, the HUS usually abates.

STEC-HUS is the most common cause of secondary HUS and the overall most common cause of HUS in the pediatric population.[5] Shiga toxin–producing bacteria, particularly the high-risk Shiga toxin 2 serotype bacteria, can precipitate this HUS.[8] The most common *E. coli* serotype is *E. coli* O157:H7. Other non-O157 STEC strains and other Shiga toxin–producing bacteria, such as *S. dysenteriae,* have also been identified.[8] The most common reservoir of *E. coli* O157:H7 is healthy cattle, which transmit *E. coli* O157:H7 through their feces. Thus, infection in humans occurs after consumption of contaminated food or water (undercooked ground beef, unpasteurized dairy products, fresh produce), person-to-person contact, or contact with carrier animals. Shiga toxin is transferred into the bloodstream from the gastrointestinal tract by attaching to the cell membrane receptor Gb3. Shiga toxin is translocated into any cell that expresses the Gb3 receptor, particularly endothelial cells.[8] Invasion of the toxin into endothelial cells precipitates cytotoxic damage. Microvascular injury initiates thrombotic responses such as platelet adhesion and microthrombi generation.[8] Damage to endothelial cells in the kidney and large bowel can explain most of the signs and symptoms of HUS. However, other organs, including the pancreas and central nervous system, can also be involved, which can have a direct correlation with the overall extent of the disease.

In the acute phase of secondary HUS, a decrease in C3 and C4 as well as an increase in complement degradation products may be observed. However, no correlation with disease severity and degree of changes in levels of C3, C4, and complement degradation products has been found.

Another cause of secondary HUS in the pediatric population is that induced by *S. pneumoniae*. The exact pathophysiology has not been determined. The neuraminidase produced by *S. pneumoniae* cleaves *N*-acetyl neuraminic acid (sialic acid), exposing the Thomsen-Friedenreich (TF) antigen on platelets, erythrocytes, and glomerular endothelial cells. Preformed immunoglobulin M antibodies react to the expressed TF antigen, precipitating the complement cascade leading to HUS.

CLINICAL ASPECTS

Clinical Manifestations

The clinical presentation of HUS is nonspecific. Signs and symptoms include weakness, fatigue, pallor, shortness of breath, decreased urine output, and severe hypertension. Systemic signs of HUS vary significantly between patients, depending on the organs affected by the HUS process. Extrarenal manifestations include but are not limited to neurologic (eg, seizures, stroke, coma), gastrointestinal (eg, hemorrhage, perforation, pancreatitis, cholestasis), pulmonary (acute respiratory distress syndrome, respiratory failure, pleural effusion), cardiac (eg, arrhythmias, ischemia, cardiomyopathy, and pericardial effusion), and endocrine (insulin-dependent hyperglycemia).

A prodromal illness with emesis, diarrhea, and abdominal pain typically precedes the development of secondary HUS precipitated by STEC. The diarrhea starts as nonbloody and progresses to bloody diarrhea in the first 3 days.[8] The microangiopathic changes occur by day 8 or 9 and anuria before day 10.[8] HUS almost always manifests 5 to 14 days after the onset of the prodrome. In *S. dysenteriae* secondary HUS, the manifestations are usually more severe. *S. pneumoniae*–induced HUS occurs in individuals with severe *S. pneumoniae* sepsis, usually presenting with complicated pneumonia and, in some cases, with meningitis.

In the setting of primary HUS, the onset of the disease may follow a trigger event such as autoimmune conditions, transplantation, pregnancy, infections, drugs, or metabolic disorders. Primary HUS presentation is usually more severe and usually relapses without directed treatment.

The hallmark of HUS disease is the classic triad of microangiopathic hemolytic anemia, thrombocytopenia, and AKI.

Rapidly progressive thrombocytopenia is the cardinal and universal hematologic abnormality in patients with HUS. However, a transient decrease in platelet count may be observed in patients with an STEC infection who do not progress to HUS.[8]

Thrombocytopenia is defined by a platelet count below 150 000/μL or >25% decline from baseline. The severity ranges from mild to severe. Despite the severity, there are usually no clinical signs of thrombocytopenia (no petechiae, purpura, or active bleeding).

Microangiopathic hemolytic anemia is caused by nonimmune red blood cell fragmentation secondary to platelet microthrombi and is characterized by anemia and markers of hemolysis as follows:

- Hemoglobin levels are usually less than 8 g/dL
- Negative direct antiglobulin test (DAT, formerly referred to as the Coombs test; DAT can be positive in the case of pneumococcal HUS)
- Peripheral blood smear with schistocytes (including helmet cells and micro spherocytes; Figure 3)
- Increased serum indirect bilirubin concentration
- Reduced serum haptoglobin concentration
- Hemoglobinuria
- Elevated serum LDH

Another constant finding is severe hypertension secondary to endothelial swelling. The severity of kidney disease

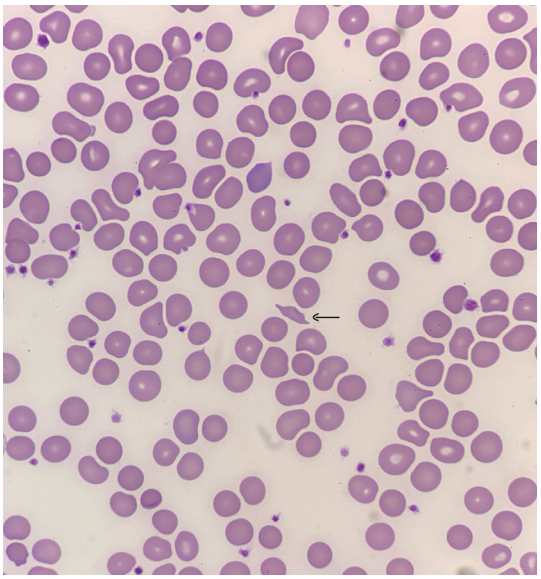

FIGURE 3. Peripheral blood smear showing an example of a schistocyte

ranges from proteinuria and microscopic hematuria to severe AKI, gross hematuria, and oliguria requiring kidney replacement therapy.

In 50% to 60% of children with secondary STEC-related HUS, oliguria is reported.[8] Hemoglobinuria is a constant finding in patients with secondary STEC-related HUS, as it reflects intravascular hemolysis that exceeds the resorptive capacity of the kidneys.

APPROACH TO DIAGNOSIS

The diagnostic approach to a patient with suspected HUS should be implemented promptly to decrease morbidity and mortality. A useful diagnostic approach for patients suspected of HUS is outlined in Figure 4. This approach relies on stepwise laboratory analysis.

Recognition of TMA is the first step in the diagnostic pathway. To do so, laboratory evaluation should include a complete blood count, peripheral blood smear, reticulocyte count, LDH level, indirect bilirubin levels, haptoglobin level, a direct antiglobulin test, and a urinalysis. Once the presence of TMA is identified, evaluation of end-organ damage should commence. For the latter, it is necessary to assess renal, cardiac, pulmonary, neurologic, and gastrointestinal function. Laboratory evaluation should include a complete metabolic panel and troponin, lactate, lipase, and liver enzyme levels. Coagulation studies, including PT, aPTT, D-dimer, and fibrinogen, should be obtained to rule out DIC. The next step should be to rule out TTP by assessing ADAMTS13 activity, which would be decreased in such disease (<10%). This step is crucial, as TTP is a medical emergency that is almost always fatal if appropriate treatment with plasmapheresis is not promptly initiated.

Once the diagnosis of HUS is established, the goal is to identify the underlying etiology. If the patient presents with a history of recent diarrhea, regardless of the presence or absence of blood in the stool, a detailed investigation for Shiga toxin–producing bacterial infection should be conducted with stool studies. A pneumococcal infection should always be considered in the pediatric population based on clinical presentation; thus, the workup should include nucleic acid tests or cultures for *S. pneumoniae*.

When primary HUS is suspected, complement activation tests should be obtained (Figure 5). Low serum C3 and normal C4 levels indicate alternative complement pathway activation. Nonetheless, this is a nonspecific and nonsensitive marker, as not all patients present with hypocomplementemia. Patients with an overactivation of the alternative complement cascade present with an elevation of the MAC, measured by soluble C5b-9. The latter is presumed to be an objective form of measuring complement activation.[4,9]

Primary HUS should be suspected when secondary HUS, TTP, or DIC are ruled out (Figure 6). At present, there is no specific diagnostic test for primary HUS. The number of new, discovered genetic abnormalities associated with primary HUS continues to increase over time, but many forms remain unknown or poorly understood. At present, 45% of the patients with primary HUS have an identifiable genetic variant.[5] Genetic workup for suspected primary HUS should include screening for complement regulator mutations and other rare causes, such as DGKε genetic variants (at least for children up to age 6 years), testing for CFH autoantibodies, and searching for inborn errors of metabolism such as cobalamin C deficiency (especially in infants younger than age 1 year).[7] Confirmation of a genetic abnormality is not required for diagnosis or management decisions of primary HUS.

In all cases of HUS, nephrology and hematology services should be consulted for appropriate management.

DIFFERENTIAL DIAGNOSIS

The diagnosis of HUS can be challenging because the syndromes TTP and DIC can mimic its presentation. The presence of microangiopathic hemolytic anemia and thrombocytopenia should prompt the search for these life-threatening conditions. TTP, DIC, and HUS share clinical manifestations and laboratory markers (Figure 6). Early recognition can facilitate the timely implementation of specific

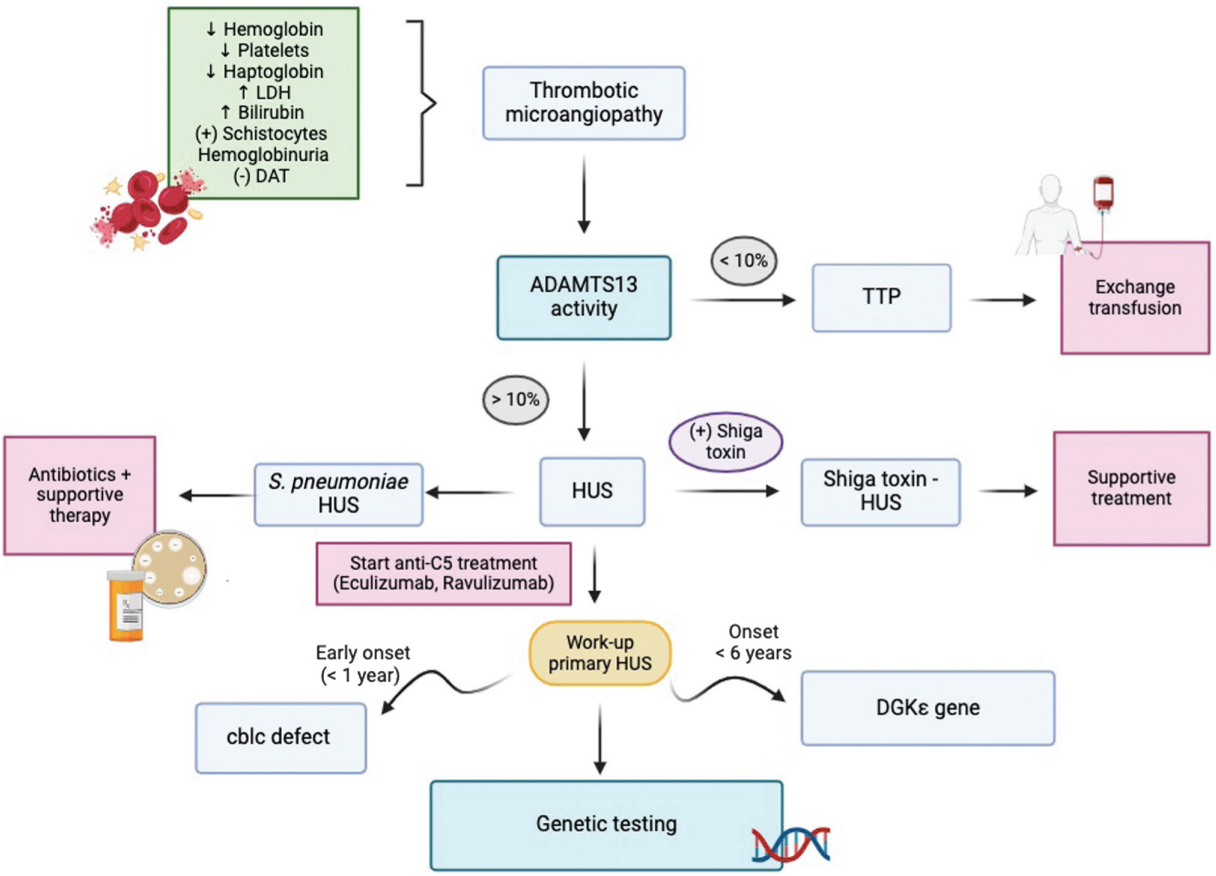

FIGURE 4. Diagnostic and therapeutic algorithm in primary TMA. ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; cblc, cobalamin C; DAT, direct antiglobulin test; DGKε, diacylglycerol kinase ε; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.

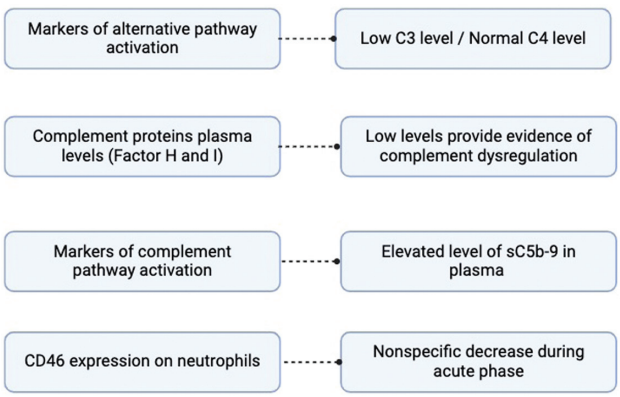

FIGURE 5. Genetic and immunological studies of the alternative complement pathway. SC5b-9, soluble terminal complement complex enzyme.

treatments. TTP usually presents later in life but can happen in childhood and usually presents with more severe thrombocytopenia, neurologic manifestations, fever, and less kidney involvement; an ADAMTS13 activity of less than 10% confirms its diagnosis. DIC is characterized by an excessive systemic activation of coagulation, resulting in hemorrhage and thrombosis. Thus, coagulation studies are usually abnormal, with high PT, high aPTT, low fibrinogen, high D-dimer, and with hemolysis being less pronounced.

	HUS	TTP	DIC
Age	Children	Adults	Any age
ADAMTS13 activity	Normal	Low (< 10%)	Normal
Hemolysis	Present	Present	Present
Platelets	Low	Very low	Low
PT/INR – PTT	Normal	Normal	Prolonged
Fibrinogen	Normal or elevated	Normal or elevated	Low
Neurologic manifestations	Not common	Present	Not common
Renal dysfunction	Present	Present	Not common
Fever	Not common	Present	Not common

FIGURE 6. Differential diagnosis: HUS, TTP, and DIC. ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; DIC, disseminated intravascular coagulopathy; HUS, hemolytic uremic syndrome; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; TTP, thrombotic thrombocytopenic purpura.

MANAGEMENT

Supportive therapy is the backbone of HUS management, which has largely contributed to the reduction in mortality once microangiopathy develops. The administration of intravenous isotonic fluids prior to the onset of HUS in patients with suspected and/or confirmed STEC infection is a simple and potentially beneficial intervention to reduce morbidity among affected children.[10] The stool of all children with a clinical picture indicative of possible STEC infection should be evaluated for pathogen detection, explicitly looking for the high-risk serotype Shiga toxin 2.[8] In children with hemodynamic instability and multiorgan dysfunction, renal replacement therapy should be considered. The replacement of packed red blood cells is generally required. However, platelet transfusions should be limited to patients with significant bleeding because HUS complications are related to thrombotic injury.[8]

In patients with STEC infection, the administration of antibiotics, narcotics, and antimotility agents has been observed to prolong the course of bloody diarrhea and increase the risk for developing HUS and neurological complications; therefore, such interventions should be strongly discouraged, and instead allow the infection to follow its self-limiting course. On the contrary, patients with a pneumococcal infection should be treated with proper antibiotic therapy to manage the specific infection.

Until recently, primary HUS was treated with plasma exchange therapy, which has variable response. Often, children would live with relapses or very severe disease leading to end-stage renal failure or death. Nowadays, the current standard of treatment for primary HUS is initiating a terminal complement blocking agent (anti-C5) such as eculizumab or ravulizumab, especially if kidney function is rapidly deteriorating during workup. These agents are humanized monoclonal antibodies against complement C5 that block the conversion of C5 to C5a and C5b, thereby preventing the generation of the MAC.[7] Of note, the blockage of the complement alternative pathway cascade puts children at risk for *Neisseria meningitidis* infection.

Even though in secondary HUS there is an overactivation of the complement cascade, it is usually self-limited when the trigger abates. Thus, the use of terminal blocking agents in secondary HUS is controversial and reserved for patients who are severely ill and for whom an underlying primary HUS cannot be fully excluded.

PROGNOSIS

With prompt recognition and appropriate supportive care, the mortality rate for STEC-HUS is less than 5% in children.[11] Such deaths are usually attributed to neurologic complications (ie, seizures, coma, or stroke). Up to 50% of patients may require kidney replacement therapy during the acute phase of the disease. Within 1 to 2 weeks, the hematologic manifestations usually resolve. Some children recover renal function completely, 5% remain dependent on dialysis, and up to 50% are left with some degree of kidney damage. Hence, patients with HUS secondary to STEC should undergo yearly follow-ups to monitor for signs of proteinuria, hypertension, and deterioration of renal function, with continued monitoring throughout adulthood. There is evidence that children with HUS secondary to STEC who initially present with high hematocrit levels (>23%) and who do not receive intravenous fluids prior to the establishment of HUS have poorer outcomes, including oliguria, the need to use kidney replacement therapy, and death.[12]

HUS that is related to pneumococcal infections is usually associated with an increase in morbidity, with more than 80% requiring dialysis and a mortality rate of up to 20%.

Primary HUS tends to be insidiously progressive with intermittent relapses. Regardless of whether a genetic abnormality

is identified, patients with primary HUS have devastating outcomes if not initiated on an anticomplement agent.[2] Although the use of anticomplement treatment in patients with primary HUS improves kidney-related outcomes, unjustified use of such therapy may be harmful. Thus, nephrology and hematology experts should always be consulted.

CONCLUSION

Primary HUS describes an underlying dysregulation of the alternative complement pathway with an underlying genetic predisposition, whereas secondary HUS is caused by some internal or external insult (infection, malignancy, transplantation, drugs, autoimmune disease). In the pediatric population, 90% of HUS cases are related to an STEC infection. However, it is essential to know that severe *S. pneumoniae* infection can also cause HUS.

Close monitoring of children with highly suspected or diagnosed STEC infection is crucial. Avoiding potentially harmful interventions and preventing volume depletion might prevent complications.

It is fundamental that pediatricians develop the ability to recognize the different signs and symptoms of HUS as well as to initiate primary evaluation. Early recognition of the underlying etiology of HUS is important for prompt treatment.

Summary

- Stool samples should be submitted for the detection of bacterial pathogens in children with hematochezia or nonbloody diarrhea accompanied by severe abdominal pain or tenesmus.[13] (Based on strong evidence.)
- Examining the peripheral blood smear for the presence of red blood cell fragmentation (ie, schistocytes, helmet cells) is necessary when HUS is suspected.[14] (Based on strong evidence.)
- Monitoring of hemoglobin, platelet count, electrolytes, and kidney function is recommended to detect early manifestations of HUS in patients with STEC infection.[14] (Based on strong evidence.)
- There is an association between dehydration and adverse outcomes in children with HUS. Thus, intravenous hydration is crucial during the diarrhea phase of STEC infection, as it reduces the risk of oliguric renal failure in those children who develop HUS.[10,14] (Based on strong evidence.)
- It is recommended to avoid the use of antibiotics in individuals infected with STEC, as there is a significant positive association between antibiotic administration and the risk of developing HUS.[14] (Based on strong evidence.)

IDEAS FOR QI PROJECTS

- Decrease the use of antibiotics in patients with acute bloody diarrhea or highly suspected STEC infection.
- Increase early aggressive intravenous hydration for patients with highly suspected STEC infection.
- Implementation of a clinical pathway for the evaluation of patients with highly suspected STEC infection and possible HUS.

Take the quiz! Scan this QR code to take the quiz, access the references, and view and save images and tables (available January 1, 2025).

PIR QUIZ

1. A previously healthy 5-year-old boy is brought to the emergency department (ED) by his parents because of a 1-day history of pallor, fatigue, swelling around the eyes, and decreased urine output. There is no associated fever, vomiting, or diarrhea. Past medical history is significant for a febrile illness 10 days ago with several episodes of nonbilious emesis, nonbloody diarrhea, and crampy abdominal pain after attending a state fair petting zoo 2 days prior. The diarrhea became bloody on the second day of illness and resolved with supportive care at home on day 3. The patient was seen in urgent care at that time and presumed to have an acute gastroenteritis. Stool studies were ordered for polymerase chain reactions and ova and parasites. The patient could not provide a stool sample in urgent care and was sent home with his parents to collect the stool sample with the next bowel movement, but the parents did not collect, as his diarrhea resolved. On physical examination in the ED today, he is afebrile with stable vital signs. Examination is remarkable for periorbital edema and pale conjunctivae. He is admitted to the hospital for further workup and management. In addition to evidence of thrombocytopenia and acute kidney injury, the presence of which of the following additional laboratory findings is most likely to confirm the diagnosis of secondary hemolytic uremic syndrome (HUS) in this patient?

   A. Cobalamin C deficiency
   B. Complement regulator mutations
   C. DGKε genetic variants
   D. Low serum C3 and normal C4 levels
   E. Microangiopathic hemolytic anemia

2. A 12-year-old girl is admitted to the hospital for management of secondary HUS that occurred after eating a hamburger from a street vendor in her neighborhood. This patient's condition is most likely caused by Shiga toxin produced by which of the following pathogens?

   A. *Campylobacter jejuni*
   B. *E. coli* O157:H7
   C. *Giardia lamblia*
   D. *Helicobacter pylori*
   E. *Salmonella typhi*

3. While rounding on the patient in the above vignette, the attending physician provides the team with an explanation of the pathophysiologic mechanism in which the Shiga toxin leads to the findings in secondary HUS. The Shiga toxin causes secondary HUS through which of the following toxin-induced pathophysiologic mechanisms?

   A. Activation of autoantibodies
   B. Cleavage of N-acetylneuraminic acid (sialic acid), exposing the Thomsen-Friedenreich antigen on platelets, erythrocytes, and glomerular endothelial cells
   C. Complement dysregulation with activation of complement alternative pathway
   D. Invasion of endothelial cells leading to endothelial cytotoxic cell damage with secondary platelet adhesion and microthrombi
   E. Severe reduction in the function of the von Willebrand factor–cleaving protease ADAMTS13, which promotes the formation of platelet microthrombi

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4. A 6-year-old boy is brought to the ED by his parents because of a 1-day history of progressively worsening watery diarrhea and crampy abdominal pain associated with fever and decreased oral intake. The last bowel movement was bloody, which prompted the ED visit. There is a history of sick contacts with multiple classmates with similar symptoms. On physical examination, his temperature is 38.8 °C. He is tachycardic with dry mucous membranes. His abdomen is diffusely tender with no rebound and hyperactive bowel sounds. The remainder of the examination is unremarkable. Stool studies were positive for *E. coli* O157:H7. Which of the following is the most appropriate next step in management?

   A. Intravenous isotonic fluids
   B. Intravenous narcotics
   C. Oral antibiotics
   D. Oral antimotility agents
   E. Oral hydration with water

5. A child is diagnosed with primary HUS. Among the following management strategies, administration of which one of the following is most likely to contribute to improved outcome in this patient?

   A. Antibiotics
   B. Fresh frozen plasma
   C. Plasma exchange therapy
   D. Red blood cell transfusion
   E. Terminal complement (C5) blocking agent