Published in final edited form as:

Pediatr Rev. 2018 February ; 39(2): 98–99. doi:10.1542/pir.2016-0112.

An Infant Presenting with Hematuria and Pallor

Lauren C. Riney, DO^{*}, Jennifer D. Treasure, MD^{*}, Charles D. Varnell Jr, MD[†], and Holly Depinet, MD, MPH^{*}

^{*}Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[†]Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

PRESENTATION

A 5-month-old healthy boy presents to our pediatric emergency department with parental concerns of blood in the urine and yellow appearance of the skin. His medical history and birth history are normal. The patient has had nonbloody diarrhea for the past 2 weeks that resolved 2 days ago. He has had 1 episode of nonbilious nonbloody emesis the previous day. In addition, he has had decreased oral intake and increased fussiness for the previous 2 days. His mother noticed a red-brown discoloration in the front of the diaper yesterday and yellow discoloration of the skin, prompting her to present to the pediatric emergency department.

Vital signs at presentation are heart rate, 157 beats/min; respiratory rate, 42 breaths/min; blood pressure, 127/70 mm Hg; and rectal temperature, 97.9°F (36.6°C). On initial examination in the emergency department, the patient is pale but alert, active, in no apparent distress, and playful. His mucous membranes are moist, and his oropharynx is normal, without lesions. The cardiovascular examination reveals a regular rate and rhythm, without murmurs, rubs, or gallops. He has strong peripheral pulses and good distal perfusion. His pulmonary examination findings are normal. His abdomen is soft, nondistended, and nontender, with normal bowel sounds. Neurologic examination shows symmetric normal strength and tone with grossly intact cranial nerves and no deficits. Skin examination shows generalized pallor but no rash or petechiae. Both feet seem to be mildly edematous.

Pertinent laboratory studies in the emergency department show a white blood cell count of 27,200/ μ L (27.2×10^9 /L) (reference range, 6,000–17,500/ μ L [6.0 – 17.5×10^9 /L]), with 38% segmented neutrophils and 2% bands; a hemoglobin level of 3.7 g/dL (37 g/L) (reference range, 10.5–13.5 g/dL [105–135 g/L]); a hematocrit level of 10% (reference range, 33%–39%); and a platelet count of 38×10^3 / μ L ($\times 10^9$ /L) (reference range, 13.5×10^3 / μ L– 46×10^3 / μ L [$\times 10^9$ /L]). In addition, the blood smear shows 2+ schistocytes, 1+ ovalocytes, and 1+ teardrops. The renal panel is significant for a potassium of level of 6.9 mEq/L (6.9 mmol/L)

Permissions & Licensing Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <http://classic.pedsinreview.aappublications.org/site/misc/Permissions.xhtml>

AUTHOR DISCLOSURE Drs Riney, Treasure, Varnell, and Depinet 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.

The Case Discussion and References appear with the online version of this article at <http://pedsinreview.aappublications.org/content/39/2/98>.

(reference range, 3.2–6.3 mEq/L [3.2–6.3 mmol/L]), a blood urea nitrogen level of 59 mg/dL (21.1 mmol/L) (reference range, 6–17 mg/dL [2.1–6.1 mmol/L]), and a creatinine level of 0.95 mg/dL (72.44 μ mol/L) (reference range, 0.16–0.39 mg/dL [12.20–29.74 μ mol/L]). The hepatic profile is normal. The urinalysis was significant for large blood and large protein with 10 to 14 white blood cells and greater than 50 red blood cells per high-power field and 2+ bacteria.

Because of severe anemia, thrombocytopenia, hyperkalemia, and acute kidney injury, the patient is admitted to the PICU and the nephrology team is consulted. Additional studies lead to the diagnosis.

DISCUSSION

While in the PICU, further laboratory studies showed a lactate dehydrogenase level of 1,704 U/L (28.5 μ kat/L) (reference range, 155–450 U/L [2.6–7.5 μ kat/L]), a haptoglobin level less than 7 mg/dL (<70 mg/L) (reference range, 16–200 mg/dL [160–2,000 mg/L]), a reticulocyte count of 5.3% (reference range, 0.5%–1.5%), a C3 complement level of 1.24 g/L (reference range 0.624 g/L–1.84 g/L), and ADAMTS13 activity of 92% (reference range, >67%). The stool culture grew *Escherichia coli* 0157:nonH7 and Shiga toxin 2 three days later. The urine culture showed no growth after 5 days. A diagnosis of hemolytic uremic syndrome (HUS) was made.

The Condition

Hemolytic uremic syndrome is a type of thrombotic microangiopathy, a heterogeneous group of diseases that have common clinical manifestations, including microangiopathic hemolytic anemia, thrombocytopenia, and organ injury. (1)(2) Classically, HUS presents as severe abdominal pain and diarrhea, often bloody, that begins several days after consumption of food contaminated with Shiga toxin–producing *E coli* (STEC). (3) Hemolytic uremic syndrome should be suspected in any pediatric patient with recent abdominal pain and diarrhea followed by thrombocytopenia and anemia 5 to 7 days later. (1) Other clinical signs during this period may include hypertension, oliguria, central nervous system manifestations, altered mental status, and possibly more severe gastrointestinal manifestations (ischemic bowel or intussusception). (4) After a few more days, anuria may develop, and the clinical picture can change to include coma, cerebral infarcts, cranial nerve dysfunction, seizures, and even death. (2)(4) Laboratory studies that should be performed on presentation are as follows: a complete blood cell count, a peripheral blood smear, renal function studies, and urinalysis. (5) Other initial testing includes coagulation studies (to differentiate from disseminated intravascular coagulation) and stool studies for Shiga toxin and cultures. (5) Shiga toxin–producing *E coli* accounts for almost 90% of all cases of HUS, with occurrence usually younger than 5 years, most being older than 6 months. (2)(3)

History has shown that young children and elderly people can have substantial impairment from infection with STEC. (6) Approximately 5% to 10% of people with STEC infection will go on to develop HUS, and 50% of those will have some degree of renal impairment after disease. (2)(6) The severity of the acute illness and the need for initial dialysis are strongly linked to a poor long-term prognosis. (7) Hemolytic uremic syndrome should be

considered for any child with a history of resolving diarrhea now with concern for kidney injury given that it is a common cause of acute renal failure worldwide. (8)

Diagnosis

The diagnosis of HUS is based on laboratory findings, although it does require a certain level of clinical suspicion, particularly given a well-appearing child with only a history of previous diarrheal illness. The most common laboratory findings are hemolytic anemia, thrombocytopenia, and renal dysfunction. (9) More specifically, the anemia found in HUS is a normochromic-normocytic anemia, with an average hemoglobin level of 8 g/dL (80 g/L). (4) Additional laboratory findings that are often seen include azotemia, a decreased haptoglobin level, an elevated C-reactive protein level, hematuria and/or proteinuria on urinalysis, an increased lactate dehydrogenase level, leukocytosis, an elevated reticulocyte count, and a negative Coombs test result. (9) The first signs of renal involvement are typically hypertension, (seen in nearly 50% of patients with HUS), hematuria, and proteinuria. (4) Severe renal disease is characterized by anuria and renal failure. (4) More commonly, however, patients experience a brief period of oliguria (median of 7 days) with associated electrolyte abnormalities, including hyponatremia, hyperkalemia, metabolic acidosis, hyperphosphatemia, and hypocalcemia. (4) A stool culture should be obtained in any patient suspected of having HUS to evaluate for the presence of STEC, which is a reportable illness and has implications for morbidity and mortality. (9)

Stool cultures were sent as well as enzyme immunoassay for Shiga toxin 1 and Shiga toxin 2 to assess for STEC-HUS. ADAMTS13 activity was sent to assess for thrombotic thrombocytopenic purpura (TTP) and in our patient was normal. The other major consideration in this patient was atypical HUS (aHUS). Given that the patient's disease was relatively mild on hospital admission, with a stable elevated creatinine level and good urine output, aHUS genetic testing was deferred unless the testing for Shiga toxin came back negative. Current diagnostic criteria for aHUS are a serum creatinine level at or above the upper limit of normal, microangiopathic hemolytic anemia, thrombocytopenia, ADAMTS13 activity of 5% or more, and negative stool tests for Shiga toxin-producing infection. Our patient's stool culture was positive for *E coli* 0157:nonH7 and Shiga toxin 2, thus, further treatment was supportive in nature.

Differential Diagnosis

In a pediatric patient presenting with a recent diarrheal illness, the differential diagnosis is broad and includes viral or bacterial gastroenteritis, colitis, inflammatory bowel disease, or intussusception. (9) In a pediatric patient presenting with laboratory findings of severe anemia, thrombocytopenia, and concern for acute kidney injury, the differential diagnosis is relatively narrow. Three diseases that were initially considered that could describe the patient's presenting symptoms include HUS, aHUS, and TTP.

By definition, aHUS is not preceded by the characteristic bloody diarrhea of STEC infection, but because most cases of aHUS involve dysregulation of the complement system it is frequently triggered by an infectious event, including gastroenteritis with diarrhea. (10)

Commonly, TTP, which is rare in children, is caused by congenital mutation in the *ADAMTS13* gene, a plasma metalloprotease that cleaves von Willebrand factor. (1)

Management

There are no known cures for HUS, and management is primarily supportive. Given the wide range of illness severity, it is important that patients diagnosed as having HUS are closely monitored for anemia, electrolyte disturbances, and acute renal failure. Fluid balance before and after the development of HUS has been shown to be important in limiting the severity of renal failure and the need for dialysis. (9) The decision to start dialysis is based on the ability to correct renal failure and electrolyte abnormalities with fluid replacement alone. (4) Approximately 50% of patients will require dialysis at some point during the illness, with approximately 7.6% going on to require dialysis long-term. (8) In addition, studies have shown that more than 90% of patients diagnosed as having HUS will require a blood transfusion during the course of the illness. (8) Regarding the finding of thrombocytopenia in HUS, platelet transfusions are not routinely given due to the worsening of the thrombotic cascade, and platelet function typically normalizes after several weeks. (4) Interestingly, the use of antibiotics has been studied in patients diagnosed as having HUS and in some studies has been shown to actually increase the incidence and complications of HUS when given during the diarrheal stage of the illness. (2)(3) The worsening of disease is believed to be secondary to the release of large amounts of bacterial toxins with the use of antibiotics. (2)(3)

Patient Course

During his PICU admission, the patient remained hemodynamically stable. He was given calcium chloride 10 mg/kg intravenously for cardiac membrane stabilization. He was kept nothing per os and started on 10% dextrose 1/2 normal saline for insensible losses at 10 mL/kg as well as replacement fluids for urine output every 6 hours. Furosemide 2 mg/kg was given intravenously due to hyperkalemia and concern for blood transfusion exacerbating his hyperkalemia. Slow correction of anemia was performed to prevent massive hemolysis. He was given 2 intravenous transfusions of packed red blood cells 5 mL/kg each. No antibiotics were given. No antihypertensives were needed because the systolic blood pressure remained less than 130 mm Hg and trended down during the admission, although still elevated for his age. Daily weights were obtained, strict intake and output were recorded, and nephrotoxins were avoided. He had good urine output during his admission. He was transferred from the PICU after 2 days to the nephrology service and was discharged after 5 days.

The patient had return of normal renal function at his nephrology outpatient visit 48 days after his initial diagnosis of Shiga toxin–positive HUS. Blood pressure was 82/50 mm Hg, which was 37 percentile systolic for age and 88 percentile diastolic for age, based on the 2000 National Health and Nutrition Examination Survey data. Laboratory studies showed normalization of his electrolytes, blood urea nitrogen, creatinine, hemoglobin, and platelets. Urinalysis was negative for proteinuria and hematuria. He had no evidence of chronic kidney disease at further follow-up visits with the nephrology service.

Lessons for the Clinician

- Hemolytic uremic syndrome is one of the most common causes of acute renal failure in the pediatric population worldwide, and its rising incidence makes it an important diagnosis to consider. (11)
- Although hemolytic uremic syndrome is a disease with specific laboratory criteria, the wide variance of clinical presentations and multiple etiologies of the illness can make it difficult to diagnose.

References

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014; 371(7): 654–666. [PubMed: 25119611]
2. Keir LS, Marks SD, Kim JJ. Shigatoxin-associated hemolytic uremic syndrome: current molecular mechanisms and future therapies. *Drug Des Devel Ther*. 2012; 6:195–208.
3. Noris M, Remuzzi G. Hemolytic uremic syndrome. *J Am Soc Nephrol*. 2005; 16(4):1035–1050. [PubMed: 15728781]
4. Corrigan JJ Jr, Boineau FG. Hemolytic-uremic syndrome. *Pediatr Rev*. 2001; 22(11):365–369. [PubMed: 11691946]
5. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol*. 2016; 31(1):15–39. [PubMed: 25859752]
6. Thorpe CM. Shiga toxin-producing *Escherichia coli* infection. *Clin Infect Dis*. 2004; 38(9):1298–1303. [PubMed: 15127344]
7. Garg AX, Suri RS, Barrowman N, et al. Long-term renal-prognosis of diarrhea associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression. *JAMA*. 2003; 290(10): 1360–1370. [PubMed: 12966129]
8. Mody RK, Gu W, Griffin PM, et al. Postdiarrheal hemolytic uremic syndrome in United States children: clinical spectrum and predictors of in-hospital death. *J Pediatr*. 2015; 166(4):1022–1029. [PubMed: 25661408]
9. Razzaq S. Hemolytic uremic syndrome: an emerging health risk. *Am Fam Physician*. 2006; 74(6): 991–996. [PubMed: 17002034]
10. Grisaru S. Management of hemolytic-uremic syndrome in children. *Int J Nephrol Renovasc Dis*. 2014; 7:231–239. [PubMed: 24966691]
11. Whyte DA, Fine RN. Acute renal failure in children. *Pediatr Rev*. 2008; 29(9):299–306. quiz 306–307. [PubMed: 18765468]