"HUS, it’s what’s for dinner": Hemolytic Uremic Syndrome

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Author: Sam Hopp, MSIII
Peer Reviewers: Travis Smith, DO, Blake Briggs, MD

Introduction
Hemolytic uremic syndrome (HUS) is a clinical syndrome characterized by an acute kidney injury with associated microangiopathic hemolytic anemia and thrombocytopenia. Infection with Shiga toxin-producing E. coli (also known as STEC) is the most common cause of HUS in the pediatric population, accounting for up to 90% of all cases in children under the age of five. The most common strain of STEC-HUS is E. Coli O157:H7, with a primary means of transmission through undercooked food (beef) and less common sources, including person-to-person or direct animal contact. Children are more affected than adults, and the causes, diagnosis, and management are essentially the same for adults and children, so we will essentially speak regarding the care of children this review.

HUS can also be classified into both acquired and hereditary causes. STEC-associated HUS mentioned is a “typical” secondary cause of HUS. Other culprits in this category include Strep pneumoniae, HIV, drug toxicities, pregnancy, or autoimmune disorders, including lupus. Primary or “atypical” HUS is a hereditary syndrome often due to complement gene mutations, antibodies to complement factor H, dicglycerol kinase epsilon gene mutations, or inborn error of cobalamin C metabolism.

It’s important for us to cover this acquired HUS, as its often misdiagnosed. In fact, one study showed that in children with STEC, 1 in 7 developed HUS within a median of 3 days, and ~30% of those who had HUS were first sent home.

Annoying, but necessary, pathogenesis
Welcome back to medical school. Remember Shiga toxin? We didn’t think you did…. So, the virulence of STEC comes from the production of Shiga toxin. The release of Shiga toxin causes widespread microangiopathic injury and a reactive prothrombotic state. The prothrombotic state and high platelet consumption leads to the formation of intravascular microthrombi, which clog the afferent vessels of the kidneys and cause acute kidney injury. The microangiopathic hemolytic anemia results from the shearing of RBCs as they pass through microthrombi, leading to the characteristic schistocytes seen on a blood smear.

Clinical Presentation
The classic prodromal illness of children with STEC-HUS is abdominal pain, nausea, vomiting, and diarrhea with or without a fever. The diarrhea is often non-bloody and turns bloody after 1-3 days. The initial illness typically resolves within a week, and complications of HUS (if occurring) arise 5-13 days after the initial onset of symptoms.

Patients presenting with pallor, decreased energy, oliguria, or edema in the setting of recent gastrointestinal illness are highly suspicious for HUS. Despite thrombocytopenia, there is rarely evidence of purpura or active bleeding. Additionally, up to 33% of patients with HUS may have CNS involvement, including AMS, seizures, coma, stroke, or hemiparesis.

Look-Alikes!
Below are some pathologies that are often mistaken for STEC-HUS on board exams. Although management of these patients may not change much in real life, it’s important to note the differences here.

<table>
<thead>
<tr>
<th>Features</th>
<th>Why not STEC-HUS</th>
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<tr>
<td>Enteric infections (ex. Salmonella, Campylobacter jejuni, Yersinia, Amebiasis) Abdominal pain, bloody diarrhea, high fever, leukocytosis +/− high BUN due to volume depletion</td>
<td>Absence of thrombocytopenia and hemolytic anemia</td>
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<td>Disseminated intravascular coagulation Classic triad (microangiopathic hemolytic anemia + thrombocytopenia + acute kidney injury)</td>
<td>+ Elevated d-dimer + Low fibrinogen + Prolonged PT/PTT?</td>
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<tr>
<td>Thrombotic thrombocytopenic purpura Hemolytic anemia, thrombocytopenia, renal involvement</td>
<td>+ Low ADAMS13</td>
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<tr>
<td>Systemic vasculitis Acute kidney injury, anemia</td>
<td>Lack of prodromal diarrheal illness + Systemic symptoms (rash, arthralgias) Peripheral &gt; central neurologic involvement</td>
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Diagnosis
The first step is a good history -- suspect STEC infection in kids with acute onset of bloody diarrhea and abdominal pain or acute onset diarrhea with known exposure to STEC patient/outbreak.

Initial labs: CBC, electrolytes (including creatinine), urinalysis, stool specimen for culture or Shiga toxin test
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- Microangiopathic hemolytic anemia:
  - Hgb < 8 g/dL with a negative Coomb’s test (you won’t have access to a Coomb’s test in the ED)
  - Peripheral smear showing up to 10% schistocytes and helmet cells
- Thrombocytopenia: platelet count below 140,000/mm³
- Acute kidney injury: variable presentation on labs, often abnormally elevated serum Cr and BUN, may have hematuria on urinalysis
- Coagulation studies to distinguish from DIC

Treatment
There is a positive association between volume depletion and reduction of adverse outcomes in volume-depleted patients.® If the patient tolerates it, be aggressive with fluids. Monitor electrolytes closely, as there is likely to pH changes and fluid shifts from the profound diarrhea.

Anemia is a common complication due to the hemolytic anemia. Stay on top of this, and perform a PRBC transfusion when Hgb level < 6-7 g/dL or Hct < 18%.® Emergent dialysis might be needed in critically ill patients.

But really, can I give antibiotics?
There is NO initial role for antibiotics. Studies have showed an increased incidence of HUS development in children with STEC when treated with antibiotics. A meta-analysis of observational studies with low risk of bias revealed a positive association of 2.24 between antibiotic use and HUS development (95% CI 1.45-3.36).® In addition, a prospective study of 259 children < 10 years of age with E coli O157:H7 STEC found that HUS occurred in 36% of children who received antibiotics versus 12% in the children who did not.® No studies have found that antibiotics reduce the symptoms or complications associated with STEC.

Prognosis
Thankfully, this has a favorable prognosis, often resolution of hematologic manifestations in 1-2 weeks with the recovery of renal function shortly following. There is a 4% mortality rate from CNS injury (edema, infarct, or brain death), hyperkalemia, coagulopathy, sepsis, heart failure, or pulmonary hemorrhage.® 5% have long-term sequelae (often stroke or end-stage renal disease).® Poor prognostic factors include: WBC >20k at presentation, persistent oliguria/anuria and prolonged dialysis, >50% of affected glomeruli on renal histology.®

References: