Hemolytic Uremic Syndrome
(Post-Diarrheal)

Disease Plan

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Last updated: June 28, 2021, by BreAnne Osborn.

Questions about this disease plan?

Contact the Utah Department of Health Bureau of Epidemiology: 801-538-6191.
CRITICAL CLINICIAN INFORMATION

<table>
<thead>
<tr>
<th>Clinical Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signs/Symptoms</strong></td>
</tr>
<tr>
<td>- Microangiopathic hemolytic anemia</td>
</tr>
<tr>
<td>- Thrombocytopenia</td>
</tr>
<tr>
<td>- Acute renal failure</td>
</tr>
<tr>
<td><strong>Period of Communicability</strong></td>
</tr>
<tr>
<td>- HUS itself is not communicable; however, HUS generally proceeds a diarrheal illness that is. See the appropriate disease plan to determine the period of communicability.</td>
</tr>
<tr>
<td><strong>Incubation Period</strong></td>
</tr>
<tr>
<td>- 1-2 weeks following diarrheal onset</td>
</tr>
<tr>
<td><strong>Mode of Transmission</strong></td>
</tr>
<tr>
<td>- None, HUS is not transmissible.</td>
</tr>
<tr>
<td>- Underlying causative agent is generally transmitted via the fecal-oral route, including foodborne, waterborne, and person-to-person transmission.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Lab Test/Timing of Specimen Collection</strong></td>
</tr>
<tr>
<td>- There is no single lab test that can diagnose HUS.</td>
</tr>
<tr>
<td>- Lab tests that can lead to diagnosis of HUS include a complete blood count, peripheral blood smear, urine proteinuria, and blood urea nitrogen (BUN) tests.</td>
</tr>
<tr>
<td><strong>Type of Specimens</strong></td>
</tr>
<tr>
<td>- Blood and urine specimens can help diagnose HUS.</td>
</tr>
<tr>
<td>- Stool specimens can identify the underlying causative agent that preceded the development of HUS.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Treatment</strong></td>
</tr>
<tr>
<td>- Supportive treatment, including hydration, electrolyte management, platelet transfusion, and red blood cell transfusion</td>
</tr>
<tr>
<td>- Dialysis is sometimes necessary.</td>
</tr>
<tr>
<td><strong>Time Period to Treat</strong></td>
</tr>
<tr>
<td>- Treatment is generally given while signs and symptoms are still present. Continued dialysis may be necessary.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contact Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isolation of Case</strong></td>
</tr>
<tr>
<td>- See the disease plan for the underlying causative agent.</td>
</tr>
<tr>
<td><strong>Quarantine of Contacts</strong></td>
</tr>
<tr>
<td>- See the disease plan for the underlying causative agent.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection Control Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Standard and enteric precautions may be necessary depending on the underlying causative agent. See the appropriate disease plan for more information.</td>
</tr>
</tbody>
</table>
WHY IS HEMOLYTIC UREMIC SYNDROME IMPORTANT TO PUBLIC HEALTH?

Hemolytic uremic syndrome (HUS) is a serious sequela of a prior infection. The most common prior infection being that of Shiga toxin-producing Escherichia coli (E. coli). On average, Utah has eight cases of post-diarrheal HUS reported each year. Occurrence of HUS could be indicative of additional cases of the source disease in the community. Correct diagnosis, confirmation of initial etiology, early detection of cases, and interview of ill persons is crucial in identifying sources of illness and preventing future cases and outbreaks.

DISEASE AND EPIDEMIOLOGY

Clinical Description
HUS is an acute illness involving the kidney and blood clotting system. HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Most cases of post-diarrheal HUS begin with a prodromal phase of acute gastrointestinal illness (usually diarrhea). Early symptoms of HUS following a gastrointestinal illness can include bloody stools, irritability, fever, lethargy, vomiting, and weakness. Later symptoms may include bruising, decreased consciousness, low or no urine output, and pale or yellow skin.

Causative Agent
HUS consists of anemia from red blood cell destruction and impaired renal function. Many different infections and disorders are associated with the development of HUS. However, it is widely accepted that Shiga toxin-producing E. coli is the most common cause of HUS. Other bacterial agents that may be associated with HUS include: Shigella, Salmonella, Yersinia, and Campylobacter. Only HUS that follows an acute diarrheal illness should be reported to public health.

Differential Diagnosis
The differential diagnosis for HUS includes disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), and systemic vasculitis.

Laboratory Identification
There is no single laboratory test for HUS. A person with HUS will usually have a history of diarrhea for a few days, with development of bloody diarrhea, anemia, and kidney failure. If a healthcare provider suspects HUS based on a patient’s symptoms, the provider will request several laboratory tests. The diagnosis of HUS depends on laboratory demonstration of:

- Anemia with microangiopathic changes, and
- Renal injury, evidenced by hematuria, proteinuria, or elevated creatinine level.

Anemia occurs when the blood has too few red blood cells, which contain an iron-rich protein called hemoglobin. In the case of HUS, the patient has too few red blood cells because the red
blood cells are being destroyed prematurely (hemolysis). Hematocrit, the test that determines the amount of red blood cells in the patient’s blood, is usually ordered as part of the complete blood count (CBC).

**Microangiopathic changes** are changes in the structure of the red blood cells that occur when they are prematurely destroyed. These cell fragments are known as schistocytes, and can take on various shapes (burr cells, helmet cells, etc.). The presence of schistocytes can be determined using a peripheral blood smear, which is usually ordered as part of the complete blood count (CBC).

**Hematuria** is blood in the urine, and can be microscopic or visible. A chemical examination of urine using small test strips will approximate the amount of blood in the urine. A positive test indicates an increased amount of red blood cells.

**Proteinuria** is characterized by protein in the urine, and can be an early sign of kidney disease. A chemical examination of urine using small test strips will measure the approximate amount of protein in the urine. A positive test indicates an increased amount of protein.

**Creatinine and urea nitrogen** are chemical waste products that are usually filtered out of the blood by the kidneys and excreted from the body in urine. These waste products can build up in the blood when the kidneys are not functioning properly. Creatinine levels and results from blood urea nitrogen (BUN) tests are used as indicators of kidney function. Increased levels of either creatinine or urea nitrogen indicate diseases or conditions that affect the kidneys. These tests are usually ordered as part of the basic or comprehensive metabolic panel (BMP or CMP) run on blood samples.

**NOTE:** Additional laboratory testing, such as stool cultures, to identify the infectious trigger of HUS should be conducted as well to determine whether *E. coli* or another bacterium is present. The combination of clinical signs and symptoms and the laboratory results help a doctor determine the diagnosis of HUS.

**Treatment**

The mainstay of treatment of patients with HUS remains supportive care. Depending on the needs of the patient, this supportive care may involve red blood cell transfusions, platelet transfusion, appropriate fluid and electrolyte management, cessation of nephrotoxic drugs, initiation of dialysis, and/or provision of adequate nutrition. There is no known therapy to halt the progression of HUS. Antibiotics are generally not recommended as they can increase risk of HUS and may make symptoms worse.

Most patients with HUS recover completely with proper and timely treatment. Additional treatment for patients with severe neurologic symptoms or multiple organ involvement may be necessary.
Case Fatality
HUS is a serious illness in both children and adults. With proper treatment, most patients will recover; however, it can be fatal or produce long term sequelae (e.g., brain damage and kidney failure). The estimated case fatality rate is 3-5%. The prognosis can be influenced by the disease that preceded it. Rates can vary by disease and serotype; about 55% of those who develop HUS as a result of *E. coli* O157:H7 (one STEC serotype most commonly associated with HUS) require dialysis, and about 5% die.

Reservoir
HUS can be caused by a number of different organisms, although Shiga toxin-producing *E. coli* is the most common. Refer to the appropriate disease plan for information on reservoirs for these organisms.

Transmission
HUS can be caused by a number of different organisms, although Shiga toxin-producing *E. coli* is the most common. Refer to the appropriate disease plan for information on transmission of these organisms.

Susceptibility
Those most at risk for developing HUS are children younger than five years of age and the elderly.

HUS can be caused by a number of different organisms, although Shiga toxin-producing *E. coli* is the most common. Refer to the appropriate disease plan for information on susceptibility to these organisms.

Incubation Period
HUS usually develops 1-2 weeks following the onset of diarrhea. In some cases, diarrhea may have resolved and the patient may appear to be improving at the time of HUS onset. Refer to the appropriate disease plan for more specific information on incubation period for associated organisms.

Period of Communicability
People with HUS may still be shedding bacteria in their stool. Refer to the appropriate disease plan for information on the period of communicability for specific associated organisms.

Epidemiology
HUS is seen worldwide, and is most often caused by a recent STEC infection. Risk of developing STEC-associated HUS varies by age and Shiga toxin (stx) profile. Six to nine percent of STEC cases develop HUS. However, children younger than five years of age are particularly susceptible, and STEC strains with the stx2 gene also increase risk of HUS. One recent study conducted in a cohort of children with STEC found the risk of HUS to be 24% in those who had an STEC strain with the stx2 gene, compared to 0% in those whose strain had the stx1 gene, and 13% in those with a strain containing both the stx1 and stx2 genes.
Shigella can also produce Shiga toxins and cause HUS, though this is not common, with the exception of Shigella dysenteriae type 1; however, it is not commonly found in the U.S. Other bacterial enteric pathogens have also been observed to precede onset of post-diarrheal HUS, though this is also uncommon.

A bacterial pathogen is often not laboratory-confirmed in cases of HUS, and therefore, the proportions of cases of HUS due to specific bacterial infections are difficult to ascertain. In the past five years, there have been an average of eight cases of post-diarrheal HUS reported each year in Utah.

✓ PUBLIC HEALTH CONTROL MEASURES

Public Health Responsibility
- Investigate all suspect cases of disease, and fill out and submit appropriate disease investigation forms.
- Provide education to the general public, clinicians, and first responders regarding disease transmission and prevention.
- Identify cases and sources of infection to prevent further transmission.
- Identify clusters or outbreaks of this disease, and determine the source.

Prevention
Personal Preventive Measures/Education
To avoid exposure to bacteria that may cause HUS and prevent transmission to others, individuals should:
- Always wash their hands thoroughly with soap and water for at least 20 seconds:
  - Before eating or preparing food;
  - After cleaning or using the toilet, or helping someone use the toilet;
  - After changing diapers;
  - After touching their pets or other animals; and
  - Frequently when ill with diarrhea or when caring for someone with diarrhea.
- Wash their own hands, as well as the child’s hands, after changing a child’s diapers.
- In a childcare setting, dispose of diapers in a closed-lid garbage can.
- Never bathe a child who is experiencing diarrhea in the same bathwater with another child.
- Not swim if experiencing diarrhea or loose stools.
- Keep raw food, such as fruits and vegetables, from becoming contaminated by animal-derived food products.
- Wash fruits and vegetables thoroughly, especially those that will not be cooked.
- Cook all ground beef and hamburgers thoroughly, and send back all undercooked hamburgers for further cooking.
- Drink only pasteurized milk, juice, and cider.
In addition to avoiding exposure to bacteria, there is some evidence that maintaining adequate hydration during the diarrheal phase of STEC can prevent the development of HUS or limit its severity.

There is also evidence suggesting that antibiotic therapy during the diarrheal phase of STEC increases risk of HUS. Therefore, antibiotics are generally not recommended for patients with STEC.

**Chemoprophylaxis**

Refer to the appropriate disease plan for information on chemoprophylaxis for specific associated organisms.

**Vaccine**

Refer to the appropriate disease plan for information on vaccine for specific associated organisms.

**Isolation and Quarantine Requirements**

**Isolation:** HUS can be caused by a number of different organisms, although Shiga toxin-producing *E. coli* is the most common. Refer to the appropriate disease plan for information on isolation for specific associated organisms.

**Hospital:** Standard and Contact precautions should be followed.

**Quarantine:** HUS can be caused by a number of different organisms, although Shiga toxin-producing *E. coli* is the most common. Refer to the appropriate disease plan for information on quarantine for specific associated organisms.

**CASE INVESTIGATION**

**Reporting**

Report any illness to public health authorities that meets any of the following criteria:

- Any person diagnosed as having hemolytic uremic syndrome.
- Any person diagnosed as having thrombotic thrombocytopenic purpura.
- Any person with hemolytic anemia and renal injury as evidenced by hematuria, proteinuria, or an elevated creatinine level.
- A person whose healthcare record contains a diagnosis of hemolytic uremic syndrome.
- A person whose death certificate lists hemolytic uremic syndrome as a cause of death or a significant condition contributing to death.

Other recommended reporting procedures:

- Report all cases of hemolytic uremic syndrome (post-diarrheal).
- Reporting should be ongoing and routine.
- In Utah, HUS cases should be reported within three working days of identification.
Table 1: Criteria to determine whether a case should be reported to public health

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Evidence</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td></td>
</tr>
<tr>
<td>Onset of illness &lt;3 weeks after onset of diarrhea</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of hemolytic uremic syndrome</td>
<td>S</td>
</tr>
<tr>
<td>Diagnosis of thrombotic thrombocytopenic purpura</td>
<td>S</td>
</tr>
<tr>
<td>Death certificate lists hemolytic uremic syndrome as a cause of death or</td>
<td>S</td>
</tr>
<tr>
<td>a significant condition contributing to death</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory Evidence</strong></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>N</td>
</tr>
<tr>
<td>Microangiopathic changes on peripheral blood smear (burr cells, helmet</td>
<td>N</td>
</tr>
<tr>
<td>cells, schistocytes)</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>O</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>O</td>
</tr>
<tr>
<td>Increased creatinine level</td>
<td>O</td>
</tr>
</tbody>
</table>

Notes:
S = This criterion alone is Sufficient to identify a case for reporting.
N = All "N" criteria in the same column are Necessary to identify a case for reporting.
O = At least one of these "O" (Optional) criteria in each category (i.e., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to identify a case for reporting. (These optional criteria are alternatives, which means that a single column will have either no O criteria or multiple O criteria; no column should have only one O.)

CSTE Case Definition
HUS 1995

Clinical description
Hemolytic uremic syndrome (HUS) is characterized by the acute onset of microangiopathic hemolytic anemia, renal injury, and low platelet count. Thrombotic thrombocytopenic purpura (TTP) also is characterized by these features, but can include central nervous system (CNS) involvement and fever and may have a more gradual onset. Most cases of HUS (but few cases of TTP) 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., greater than or equal to 1.0 mg/dL in a child younger than 13 years of age or greater than or equal to 1.5 mg/dL in a person 13 years of age and older, or greater than or equal to 50% increase over baseline).
**Hemolytic Uremic Syndrome**: Utah Public Health Disease Investigation Plan

**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 seven days after onset of the acute gastrointestinal illness is not less than 150,000/mm³, other diagnoses should be considered.

**Case classification**

**Probable**:
- An acute illness diagnosed as HUS or TTP that meets the laboratory criteria in a patient who does not have a clear history of acute or bloody diarrhea in preceding three weeks, OR
- An acute illness diagnosed as HUS or TTP, that a) has onset within three weeks after onset of an acute or bloody diarrhea and b) meets the laboratory criteria except that microangiopathic changes are not confirmed.

**Confirmed**: an acute illness diagnosed as HUS or TTP that both meets the laboratory criteria and began within three weeks after onset of an episode of acute or bloody diarrhea.

**Comment**
Some investigators consider HUS and TTP to be part of a continuum of disease. Therefore, criteria for diagnosing TTP on the basis of CNS involvement and fever are not provided because cases diagnosed clinically as post-diarrheal TTP also should meet the criteria for HUS. These cases are reported as post-diarrheal HUS. Most diarrhea-associated HUS is caused by Shiga toxin-producing *Escherichia coli*, most commonly *E. coli* O157. If a patient meets the case definition for both Shiga toxin-producing *E. coli* (STEC) and HUS, the case should be reported for each of the conditions.

**Classification Table**
Table of criteria to determine whether a case is classified.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Confirmed</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Evidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Onset of illness &lt;3 weeks after onset of diarrhea</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Diagnosis of hemolytic uremic syndrome</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Diagnosis of thrombotic thrombocytopenic purpura</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td><strong>Laboratory Evidence</strong></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Anemia</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Microangiopathic changes on peripheral blood smear (burr cells, helmet cells, schistocytes)</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hematuria</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Increased creatinine level</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

**Notes:**
- N = All "N" criteria in the same column are Necessary to classify a case.
- A = This criterion must be absent (e.g., NOT present) for the case to meet the classification criteria.
O = At least one of these "O" (Optional) criteria in each category (e.g., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to classify a case.

Some investigators consider HUS and TTP to be part of a continuum of disease. Therefore, criteria for diagnosing TTP on the basis of central nervous system involvement and fever are not provided because cases diagnosed clinically as post-diarrheal TTP also should meet the criteria for HUS.

More information on what should be reported to public health, case definition, and case classification guidelines for HUS can be found here: https://cdn.ymaws.com/www.cste.org/resource/resmgr/PS/09-ID-37.pdf.

**Outbreaks**

CDC defines a foodborne outbreak as, "an incident in which two or more persons experience a similar illness resulting from the ingestion of a common food." Since HUS can have multiple causes, it is crucial that the agent which caused the disease is identified in order to link cases of HUS to each other.

**Identify Case Contacts**

HUS can be caused by a number of different organisms, although Shiga toxin-producing *E. coli* is the most common. Refer to the appropriate disease plan for information on identifying case contacts for specific associated organisms.

**Case Contact Management**

**Childcare, School, and Food Service**

A case of HUS in a childcare, school, or food service setting may be a marker for additional gastrointestinal infections within the facility. Surveillance for gastrointestinal illness should be heightened, and persons with gastrointestinal symptoms should be referred to their healthcare providers for appropriate testing.

If the case has been diagnosed with a bacterial infection, refer to the appropriate disease plan for additional information on case contact management.

**ACKNOWLEDGEMENTS**

We would like to acknowledge Virginia Department of Health for select content of this document.
REFERENCES


✔ VERSION CONTROL

Updated November 2014—CSTE reporting criteria, case definition, and case classification swim lanes included.

Updated February 2016 – Added "Why is Hemolytic Uremic Syndrome Important to Public Health" section. Updated symptoms in "Clinical Description" section. Updated “Differential Diagnosis” and "Laboratory Identification." Updated "Treatment" to include supportive care examples. Updated “Susceptibility” and “Period of Communicability” sections. Updated “Epidemiology” section with Utah trends. Reorganized “Prevention measures and recommendations.” Updated “Isolation and Quarantine Requirements” and “Case Investigation Process” to refer back to appropriate disease plan. Updated "Identify Case Contacts" section and separated from "Case Contact Management." Added "Acknowledgements," "Version Control," and "Minimum Data Set" sections. Deleted the symptoms from the Reporting Table swim lanes because there were no letter criteria associated with them and they were not in the narrative.

Updated June 2021: Updated Utah’s average case count. Added additional information to help explain why each test is ordered and what test results mean. Added information on when additional treatment may be necessary. Added/updated case fatality statistics. Updated epidemiology section, added information about Shiga toxin profiles and risk of HUS, and added information about Shigella and risk of HUS. Added recommendation to not swim with diarrhea/loose stools, and for children experiencing diarrhea to not bathe with other children. Added information about hydration as possible prevention of HUS, and antibiotics increasing risk of HUS. Added information on what forms to use in investigation. Combined information for childcare facilities, schools, and food service facilities.
**UT-NEDSS/EPITRAX MINIMUM/REQUIRED FIELDS BY TAB**

**Demographic**
- First Name
- Last Name
- Street Number
- Street Name
- City
- State
- County
- Zip Code
- Date of Birth
- Area Code
- Phone Number
- Birth Gender
- Ethnicity
- Race
- Name of facility where patient handled food
- Location
- Did the patient work while ill?
- Important information including dates

**Clinical**
- Disease
- Onset Date
- Visit Type
  - (if inpatient) Did HUS cause hospitalization?
- Date Diagnosed
- Died
  - (if yes) Date of Death
  - (if yes) Did HUS cause death?
- Name of healthcare facility
- Location
- Did the patient work while ill?
- Important information, including dates

**Laboratory**
- Lab Name
- Lab Test Date
- Collection Date
- Specimen Source
- Test Type
- Organism
- Test Result
- Accession Number
- Name of the childcare facility
- Location
- Did the patient work/attend while ill?
- Important information, including dates

**Epidemiological**
- Food Handler
- Name of facility
- Location
- Did the patient work while ill?
- Important information, including dates

**Investigation**
- Diarrheal onset date:
- HUS/TTP onset date:
- Is HUS/TTP onset date within 3 weeks of diarrheal onset date?
- Was diarrhea illness diagnosed with stool culture?
  - (if yes) Cause of HUS/TTP:
  - (if other) Specify:
- Was diarrhea treated with antibiotic(s)?
  - (if yes) List Antibiotic(s):
  - (if yes) Dose(s):
  - (if yes) Start date(s):
  - (if yes) End date(s): (Note if antibiotic is not finished)

**Reporting**
- Date first reported to public health

**Administrative**
- State Case Status (completed by UDOH)
- Outbreak Associated
- Outbreak Name