Hemolytic Uremic Syndrome (HUS), post-diarrheal
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Overview[1,2]

Hemolytic uremic syndrome (HUS), post-diarrheal is serious sequela of enteric infection with Shiga toxin-producing *Escherichia coli* (STEC). In the United States, the conditions occur more frequently with *E. coli* O157:H7 infections than with other STEC serotypes. The onset of HUS typically occurs during the two weeks following onset of diarrhea. HUS can also occur following infection with *Shigella dysenteriae* type 1 and (rarely) other bacteria. *Shigella dysenteriae* type 1 is most common in developing countries.

HUS is defined by the presence of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal dysfunction. Ninety percent of cases of HUS occur in children. Up to 20% of children with *E. coli* O157:H7 diarrhea progress to HUS, which causes kidney failure requiring dialysis in approximately 50% of patients. A total of 3-5% of patients diagnosed with HUS die. Children under 5 years of age are at greatest risk of developing HUS, although the elderly are also at increased risk of complications. Children with diarrhea-associated HUS may develop diabetes mellitus during their acute illness or afterwards. In adults, a similar condition called thrombotic thrombocytopenic purpura (TTP) may follow STEC infection. In addition to the manifestations of HUS described above, TTP may include neurologic abnormalities and fever. Clinical differentiation of HUS and TTP can be problematic and differentiation is often based on the presence of centeral nervous system (CNS) involvement in TTP and the more severe renal involvement in HUS.

Patients with HUS should be cultured for enteric pathogens, including STEC, *Shigella dysenteriae*, and *Campylobacter jejuni*. In addition, testing for the presence of Shiga toxin should be done. The absence of STEC or Shiga toxin in feces does not preclude the diagnosis of STEC-associated HUS, since HUS typically is diagnosed a week or more after onset of diarrhea, when the organism may no longer be detectable in stool.

For more information on STEC, see the section in this manual for Shiga toxin-producing *E. coli* (STEC).

For a complete description of HUS, refer to the following texts:

- *Control of Communicable Diseases Manual*. (CCDM), American Public Health Association. 19th ed. 2008.
- American Academy of Pediatrics. *Red Book: 2009 Report of the Committee on Infectious Diseases.* 28th ed. 2009.

Case Definition[3]

Clinical description:
Hemolytic uremic syndrome (HUS), post-diarrheal is characterized by the acute onset of microangiopathic hemolytic anemia, renal injury, and low platelet count. Thrombotic thrombocytopenic purpura (TTP) is also 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., $\geq$1.0 mg/dL in a child aged <13 years or $\geq$1.5 mg/dL in a person aged $\geq$13 years, or $\geq$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 seven (7) days after onset of the acute gastrointestinal illness is not <150,000/mm^3, other diagnoses should be considered.

Case classification:
Confirmed: An acute illness diagnosed as HUS or TTP that both meets the laboratory criteria and began within three (3) weeks after onset of an episode of acute or bloody diarrhea.
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 (3) weeks, OR
- An acute illness diagnosed as HUS or TTP that a) has onset within three (3) weeks after onset of an acute or bloody diarrhea and b) meets the laboratory criteria except that microangiopathic changes are not confirmed.

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 should also 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.

Information Needed for Investigation

Verify the diagnosis. Obtain demographic, clinical and laboratory information on the case from the attending physician, hospital, and/or laboratory. Obtain the information necessary to complete the "Disease Case Report" (CD-1), "Record of Investigation of Enteric Illness" (CD-2C), and the "HUS Investigation Report".

When investigating a suspected outbreak of gastrointestinal illness of unknown etiology, see the Outbreak Investigation section of the CDIRM.

Establish the extent of illness. Determine whether household or other close contacts are, or have been, ill with diarrhea, by contacting the health care provider, patient or family member. If persons with diarrhea are identified, see the section in this manual on Shiga toxin-producing *E. coli* (STEC) / Shiga toxin positive, unknown organism, or the section on Shigella or Campylobacter if appropriate.

Identify the most likely source of infection and risk factors for spread of the disease that caused HUS, in order to prevent other cases.

- Does the case or a member of the case's household attend a child care center or nursery school?
- Does the case or a member of the case's household work as a food handler or healthcare provider?
- Identify symptomatic household and other close contacts and obtain stool specimens.
- Has the case traveled prior to onset of illness? *Shigella dysenteriae, Campylobacter jejuni* or other travelers' diarrhea can be associated with HUS.
- Has the case had contact with livestock or other animals?
- Has the case prepared or consumed undercooked hamburger?
- Has the case consumed unpasteurized milk, other dairy products, or fruit juices?
- Has the safety of the drinking water been determined?
- If they safety of drinking water is in doubt, has the Department of Natural Resources been notified (public water supply) or the DHSS Bureau of Environmental Health Services (private water supply) and has a boil order-been issued?
- Does the case engage in other practices that would put them or others at increased risk?

Notification

Immediately contact the District Communicable Disease Coordinator, the Senior Epidemiology Specialist for the District, or the Department of Health and Senior Services' Situation Room (DSR) at 800-392-0272 (24/7), if an outbreak* of STEC is suspected. If a case is in a high-risk setting or job such as food handling, child care or health care contact the District Communicable Disease Coordinator and the appropriate Bureau(s) as listed below.

- Contact the Bureau of Environmental Health Services (BEHS) at (573) 751-6111, and the Section for Child Care Regulation at (573) 751-2450, if a case is associated with a child care center.

- Contact BEHS at (573) 751-6111 when a case is a foodhandler.
- Contact the Section for Long Term Care Regulation at (573) 526-8505, if a case is associated with a long-term care facility.
- Contact the Bureau of Health Services Regulation at (573) 751-6303, if a case is associated with a hospital or hospital-based long-term care facility, or ambulatory surgical center**.**
- Contact the Department of Natural Resources, Public Drinking Water Branch at (573) 751-1187, if cases are associated with a public water supply, or DHSS's Bureau of Environmental Health Services at (573) 751-6111, if cases are associated with a private water supply.

*Outbreak is defined as the occurrence in a community or region, illness(es) similar in nature, clearly in excess of normal expectancy and derived from a common or a propagated source.

Control Measures

There are no specific control measures for HUS. However, if enteric cultures are positive or the case of HUS/TTP is epidemiologically linked to a confirmed case of a specific pathogen, the control measures for that specific pathogen should be followed. See the appropriate pathogen specific section of this manual.

Laboratory Procedures

Collect clinical specimens in Cary-Blair media using the Enteric Specimen collection kit supplied by the State Public Health Laboratory (SPHL). Specimens should be shipped refrigerated. The only clinical specimen the SPHL will test is a stool sample. The SPHL will identify Shiga toxin-producing *E. coli*, *Shigella dysenteriae* and *Campylobacter jejuni* from cultures submitted by other laboratories. For epidemiological purposes, the cultured organism should be further characterized by the SPHL. The SPHL does this testing at no charge to the submitter.

Reporting Requirements

Hemolytic Uremic Syndrome, post diarrheal is a Category 2(A) disease and reportable to the local health authority or to the Missouri Department of Health and Senior Services within one (1) calendar day of first knowledge or suspicion by telephone, facsimile or other rapid communication.

1. For confirmed and probable cases, complete a "Disease Case Report" (CD-1), and a "Hemolytic Uremic Syndrome Investigation Report."
2. Entry of the completed CD-1 into the WebSurv database negates the need for the paper CD-1 to be forwarded to the District Health Office.
3. Send the completed secondary investigation form to the District Health Office.
4. All outbreaks or suspected outbreaks must be reported immediately (by phone, fax, or e-mail) to the District Communicable Disease Coordinator. This can be accomplished by completing the Missouri Outbreak Surveillance Report (CD-51).
5. Within 90 days from the conclusion of an outbreak, submit the final outbreak report to the District Communicable Disease Coordinator.

References:

1. American Public Health Association. (2008). Diarrhea, *E. coli*; Diarrhea caused by enterohemorrhagic strains. In D. Heymann (Ed.), *Control of communicable diseases manual* (19th ed., pp. 181-186). Washington, DC: American Public Health Association.
2. American Academy of Pediatrics. (2009). *Escherichia coli* diarrhea. In L.K. Pickering (Ed.) *Red Book: 2009 Report of the Committee on Infectious Diseases* (28th ed., pp. 294-298). Elk Grove Village, IL: American Academy of Pediatrics.
3. Centers for Disease Control and Prevention. (2009). Case definitions for infectious conditions under public health surveillance, 1996. http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/hemolyticcurrent.htm (6/10/2011)

Other Sources of Information

1. Donnenberg, M.S. (2010). Enterobacteriacea. In G.L. Mandell, J.E. Bennett & R.D. Dolin (Eds.), *Principles and practice of infectious diseases: Vol. 2*. (7th ed., pp. 2820-2826). Philadelphia: Elsevier Churchill Livingstone.