Hemolytic Uremic Syndrome (HUS) Investigative Guidelines

May 2024

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. Determine the incidence of HUS
2. Monitor trends in STEC infection using HUS incidence as a marker (refer to STEC guidelines for details on STEC)
3. Identify STEC strains that cause HUS and monitor changes in their frequency over time

1.2 Clinician Reporting Requirements

1. Hemolytic uremic syndrome (HUS) is a reportable clinical diagnosis that can occur as sequala of STEC infection (refer to STEC Investigative Guidelines); clinicians must report HUS cases regardless of identification of a specific etiologic agent. Laboratories rarely, if ever identify HUS. We depend on clinicians to report.

1.3 Local Health Department Reporting and Follow-Up Responsibilities

1. Report all confirmed, presumptive, and suspect HUS cases to the Oregon Public Health Division (PHD) Acute and Communicable Disease Prevention (ACDP) Section by creating a case in Orpheus within one working day of the initial report. See §3 for HUS case definitions.
2. Begin investigation within one working day following case identification. Enter information into Orpheus as investigation progresses. Enter date in “LHD Completion Date” box in Orpheus (bottom left of home page) when investigation is complete.
3. If an STEC isolate is not recovered, the Shiga toxin-positive broth, or specimen, should be forwarded to OSPHL for additional testing (refer to STEC Investigative Guidelines).

A Note about HUS Reporting

The requirement to report HUS (a separate case report from STEC) is an indirect way of finding otherwise unreported STEC infections, and secondarily a way to learn about other potential causes of HUS. These cases are identified clinically by the attending physician, typically a nephrologist or gastroenterologist. HUS cases can occur in various contexts:

- Secondary to a confirmed STEC infection: follow up as for any other STEC case.
- Secondary to a presumptive STEC infection: consult with ACDP epidemiologists regarding testing options to confirm etiology; otherwise follow up as for any other STEC case.
- Not following diarrheal illness and with no epidemiologic link to any STEC cases: consult with ACDP epidemiologists.

The following guidelines generally presume you are investigating STEC-related illness, including that caused by O157 and non-O157 serogroups.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 HUS and thrombotic thrombocytopenic purpura (TTP)

Hemolytic uremic syndrome (HUS) entails microangiopathic hemolytic anemia, thrombocytopenia, and elevated creatinine. Early clinical signs of HUS may include decreased urine output, pallor, and lethargy. Persons with HUS have variable degrees of renal insufficiency; some may eventually need dialysis (short- or long-term) or even transplant. There is also a greatly increased risk of stroke and other complications. STEC infection is the principal cause of reported cases of HUS, particularly for children.

About 75% of HUS cases in the U.S. can be linked to laboratory-verified STEC, usually O157.[1] After 3–10 days of illness, about 15% of children diagnosed with O157 STEC—usually patients <5 years of age—develop hemolytic uremic syndrome (HUS).[1] Children with bloody diarrhea should be closely monitored for the development of HUS. If a complete blood cell count with smear, blood urea nitrogen, and creatinine are normal 3 days after the resolution of diarrhea, it is unlikely that HUS will develop. Adults with O157 STEC can also develop HUS, but far less commonly than children do; however, older adults with HUS have the highest risk of death.[1]

Although the O157:H7 serotype is most often associated with hospitalization and HUS, non-O157 STEC infections can also result in these outcomes.[2] Up to 22% of adults diagnosed with particularly virulent strains of non-O157 STEC progress to HUS.[1] Consequently, non-O157 STEC infections should be treated as aggressively as O157:H7 infections.

Hemolytic uremic syndrome (HUS) is a complication of STEC infection that overlaps with thrombotic thrombocytopenic purpura (TTP). Thrombotic

thrombocytopenic purpura (TTP) is similar to HUS, but with the addition of prominent neurologic signs (seizures, confusion, etc.). TTP primarily affects adults and should be reported so that patients can be evaluated as potential STEC cases.[1] Although it is uncommon, HUS or TTP caused by STEC can occur without antecedent diarrheal illness. Refer to §3 for HUS case definitions. See the CSTE position statement[3] for extended discussion of HUS versus TTP.

3. CASE DEFINITIONS, DIAGNOSIS, AND LABORATORY SERVICES

Investigation of STEC cases must include ascertainment of whether HUS also developed. HUS may uncommonly be reported in the absence of documented STEC infection.

3.1 Confirmed Case of HUS

- An acute illness diagnosed as HUS or TTP that meets the laboratory criteria (See §3.4) AND began within 3 weeks after onset of an episode of acute or bloody diarrhea.

3.2 Presumptive Case of HUS

- An acute illness diagnosed as HUS or TTP that meets the laboratory criteria (See §3.4) in a patient who does not have a clear history of acute or bloody diarrhea in preceding 3 weeks, OR

- An acute illness diagnosed as HUS or TTP, that has onset within 3 weeks after onset of an episode of acute or bloody diarrhea AND meets the laboratory criteria (See §3.4) except that microangiopathic changes are not confirmed.

3.3 Suspect Case of HUS

- An acute illness diagnosed as HUS with evidence of STEC infection (clinical specimen is culture- or CIDT-positive) but without documented laboratory criteria (See §3.4).
- Confirmed or probable HUS case as defined above except that no microangiopathic changes are observed or are missing or unknown (See §3.4).

3.4 Laboratory Criteria (both anemia and renal injury must be present at some time during illness)

- Anemia[4] (acute onset), as defined by hematocrit (HCT)*, with microangiopathic changes (i.e., schistocytes, burr cells, or helmet cells) on peripheral blood smear

  *Anemia (Defined by hematocrit [HCT]; if HCT missing, 3*hemoglobin used):
  - All children age ≤5: HCT <32.9
  - All children age 6–11: HCT<34.5
  - male age 12–14: HCT<37.3
  - male age 15–17: HCT< 39.7

- male age ≥18: HCT<39.9
- female age 12–14: HCT<35.7
- female age15–17: HCT<35.9
- female age ≥18: HCT<36

- Renal injury (acute onset) evidenced by either hematuria, proteinuria, or elevated creatinine level (i.e., ≥1.0 mg/dL in a child aged <13 years or ≥1.5 mg/dL in a person aged ≥13 years

3.5 Services available at the Oregon State Public Health Laboratory (OSPHL)

Almost all persons with HUS develop antibodies to the O antigen of the STEC bacterium. For persons with HUS who are culture- and CIDT-negative for STEC, arrange for a leftover serum sample to be tested for STEC antibodies at CDC. Two to six weeks after onset is the best time to draw; consult with ACDP epidemiologists.

REFERENCES

1. Heymann DL, ed. *Control of Communicable Diseases Manual*. 21st ed. APHA Press; 2022.

2. Valilis E, Ramsey A, Sidiq S, DuPont HL. Non-O157 Shiga toxin-producing Escherichia coli-A poorly appreciated enteric pathogen: Systematic review. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis*. 2018;76:82-87. doi:10.1016/j.ijid.2018.09.002

3. Council of State and Territorial Epidemiologists. *HUS Case Definition*. Council of State and Territorial Epidemiologist; 1995. https://www.cste.org/page/PositionStatements

4. Centers for Disease Control and Prevention. FoodNet, HUS Surveillance Protocol, January 2024.

UPDATE LOG

May 2023 – Created HUS Investigative Guidelines with CSTE and FoodNet criteria for case ascertainment (R. Trevejo).