Haemolytic Uremic Syndrome

Revision Dates

Case Definition	April 2013
Reporting Requirements	April 2013
Remainder of the Guideline (i.e., Etiology to References sections inclusive)	April 2013

Haemolytic Uremic Syndrome (HUS) is a distinct clinical syndrome that has many triggers that can be both infectious and non-infectious in nature. Typical HUS usually occurs after a prodrome of diarrhea (D^+HUS) and atypical HUS is not associated with a diarrheal prodrome (D^-HUS).

Only HUS associated with an *infectious causative organism* is reportable to Alberta Health.

Case Definition

Clinical Case - Confirmed

An acute illness diagnosed as HUS[1] that:

- meets both the laboratory criteria[2] AND
- begins within 3 weeks after onset of a diarrheal illness (usually bloody diarrhea), OR less commonly after a non-diarrheal illness, caused by an infectious organism AND
- occurs in the absence of chronic underlying conditions that may account for renal and haematological dysfunctions.

**The following probable case definition is provided as a guideline to assist with case finding and public health management and should not be reported to Alberta Health.*

Clinical Case - Probable *

An acute illness diagnosed as HUS[1] that:

- meets the laboratory criteria[2] BUT
- without laboratory confirmation of an infectious organism causing a preceding illness.

[1]HUS is defined by the triad of microangiopathic haemolytic anemia, thrombocytopenia (low platelet count) and acute renal impairment. Most cases of HUS occur after an acute gastrointestinal illness (usually bloody diarrhea).

[2]The following are present at some time during the course of the illness (they may not all be present simultaneously):

- Acute renal impairment evidenced by elevated serum creatinine levels as follows[3] or as determined in consultation with the attending physician:
  - > 50 µmol/L if < 5 years
  - > 60 µmol/L if 5 – 9 years
  - > 90 µmol/L if 10 –13 years
  - > 110 µmol/L if > 13 years
- Microangiopathic haemolytic anemia (Hb < 100g/L with fragmented red cells)
- Thrombocytopenia (< 150 000 x 10^9/L) in the absence of septicaemia, malignant hypertension, chronic uremia, collagen or vascular disorders

[3]Laboratory parameters adapted from Canadian Paediatric Society (1)
www.web.cps.ca/English/surveillance/cpsp/Studies/hemolytic.htm

Reporting Requirements

1. **Physicians, Health Practitioners and others**
   Physicians, health practitioners and others listed in Sections 22(1) or 22(2) of the *Public Health Act* shall notify the Medical Officer of Health (MOH) (or designate) of all confirmed cases in the prescribed form by mail, fax or electronic transfer within 48 hours (two days).

2. **Alberta Health Services and First Nations and Inuit Health Branch**
   - The MOH (or designate) of the zone where the case currently resides shall forward the preliminary Notifiable Disease Report (NDR) of all confirmed cases to the Chief Medical Officer of Health(CMOH) (or designate) within two weeks of notification and the final NDR (amendment) within four weeks of notification.
   - For out-of-zone reports, the MOH (or designate) first notified shall notify the MOH (or designate) of the zone where the client currently resides by mail, fax or electronic transfer within 48 hours (two days).
   - For out-of-province and out-of-country reports, the following information should be forwarded to the CMOH (or designate) by phone, fax or electronic transfer within 48 hours (two days) including:
     - name,
     - date of birth,
     - out-of-province health care number,
     - out-of-province address and phone number and
     - attending physician (locally and out-of-province).

Etiology

Haemolytic uremic syndrome can be classified as diarrhea-associated (D^+ HUS) or non-diarrhea-associated or atypical (D^- HUS).(1)

Verotoxigenic *E. coli* (VTEC) serotype O157:H7 is thought to cause >90% of cases of D^+HUS in North America however, illnesses caused by other infectious organisms such as *Shigella dysenteriae* can also lead to HUS.(2) D^-HUS has been associated with various non-enteric infections, viruses, drugs, malignancies, transplantation, pregnancy, autoimmune disorders and other underlying medical conditions.(3) HUS can also occur sporadically or within families.(4) Infections caused by *Streptococcus pneumoniae* have been linked to 40% of D^-HUS cases.(3, 5)

NOTE: Verotoxigenic *E. coli* (VTEC) may also be referred to as verotoxin-producing *E. coli*, enterohaemorrhagic *E. coli* (EHEC), Shiga toxin-producing *E. coli* (STEC) and verocytotoxin-producing *E. coli*.

Clinical Presentation

Haemolytic uremic syndrome (HUS) is a clinical syndrome characterized by acute renal failure, haemolytic anemia and thrombocytopenia.(1) The initial prodromal clinical presentation will vary depending on the infecting organism (refer to specific guidelines, e.g., *Escherichia coli* Verotoxigenic Infections, Shigellosis, Invasive Pneumococcal Disease).

Approximately 15% of children with *E. coli* O157:H7 diarrhea and a smaller proportion of adults develop HUS. 50% of patients will require dialysis and as high as 5% will die. Rates differ for other serotypes.(1) HUS is a microangiopathic, haemolytic anemia with the kidneys being the most vulnerable target organ. However, any tissue can be affected and become ischemic from capillary and large vessel thrombosis. Other organs which may potentially be affected include the brain (stroke), pancreas (pancreatitis) and colon (ischemic colon).(6)

HUS is the most common cause of acute renal failure in young children.(6, 7, 8) The illness can be life threatening and typically develops within the first week (up to 3 weeks) after onset of hemorrhagic (bloody) diarrhea in VTEC infections.(9) Initial symptoms of VTEC infections include severe abdominal pain and non-bloody diarrhea which usually progresses to bloody diarrhea. Fever occurs in less than 1/3 of cases. Hemorrhagic colitis can result from severe infections.(9) Gastrointestinal symptoms may resolve before the onset of anemia and renal failure symptoms of HUS. The anemia and uremia usually presents with pallor, lethargy and irritability. Other symptoms may include hypertension, oliguria, edema and macroscopic hematuria.(7) Neurological complications such as seizure, stroke and coma can occur in 25% of HUS patients as well as chronic renal sequelae, usually mild.(10)

Atypical HUS, (D^-HUS) cases can occur following non-specific, non-diarrheal illnesses and without a seasonal tendency.(5) Individuals may have a slow, progressive course, with an insidious development of HUS. Neurological symptoms with convulsions and alterations of consciousness can be more often seen. Children will have hypertension at onset. Renal involvement will be exhibited by oliguria or anuria, high renal retention values or degradation of the creatinine clearance.(8) There may be a familial aspect to atypical HUS and has a worse long-term prognosis as compared to typical HUS.

Diagnosis

Diagnosis of HUS is based on clinical history, physical exam and laboratory manifestations as outlined in the case definition.

Epidemiology

Incidence of *E .coli* O157:H7 infections and HUS are increased in the summer and fall months. This may or may not be attributed to seasonal environmental or food exposures, or to seasonally varying levels of contamination from these or other vehicles of transmission.(11)

Reservoir

This will depend on the etiologic agent. Refer to the specific guideline.

Transmission

This will depend on the etiologic agent. Refer to the specific guideline.

Incubation Period

This will depend on the etiologic agent. Refer to the specific guideline.

Period of Communicability

This will depend on the etiologic agent. Refer to the specific guideline.

Host Susceptibility

People of any age can be affected but children under 5 years of age and the elderly are at greatest risk of developing VTEC/STEC induced HUS.(2, 6) Atypical HUS (non-diarrhea associated) may occur at all ages but it is more frequently seen in adults and prognosis is generally poorer.(8)

Occurrence

General

E. coli infections and HUS appear to be more prevalent in the Northern Hemisphere and in latitudes farther away from the equator however, there are notable exceptions. Buenos Aires and Argentina which are both below the equator have a high prevalence of HUS cases.(11) This is related to their strong beef industry.(18) In 2004, the overall rate of *E. coli* O157:H7 infection for Canada was 3.36 per 100,000 persons, while Alberta's rate was more than double at 8.96 per 100,000 persons.(12) Cattle serve as a recognized reservoir for *E. coli* O157, as the organism can reside asymptomatically in the animal's intestinal tract.(13) The principle source of human infection is due to fecal contamination of food and water sources. Studies have shown a spatial association between cattle density and the incidence of human *E. coli* O157 infection.(14)

In countries that lack the resources for diagnosis of the infection, rates of *E. coli* infections are probably underestimated.(11)

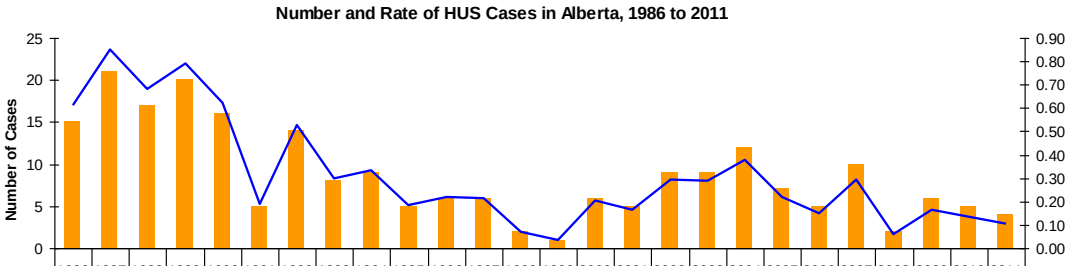
In the spring of 2012, a large outbreak of severe illness caused concern in Germany with reported deaths and increased numbers of HUS cases. The pathogen associated with this outbreak is *E. coli* O104. The outbreak was unusual, in that it developed very quickly and affected high numbers of adults particularly women, instead of the normal high-risk groups which are young children and the elderly.(10)

Canada

HUS is not currently nationally notifiable. The Canadian Paediatric Surveillance Program (CPSP) conducted surveillance on incidence of HUS from April 2000 – March 2002. Based on the CPSP case definition, 140 confirmed cases of HUS were reported to December 31, 2002. Study data indicated that $HUS^{+}D$ constituted a significant public health concern in Canadian children <5 years of age. Median age was 3.7 years (0.08-15.5). From the 121 completed reports received, most children with $HUS^{+}D$ were within the 1 – 4 years age group: <1 year (7%); 1 – 4 years (56%); 5 – 9 years (26%); 10 – 15 years (11%). Based on population figures from Statistics Canada at the time, the incidence of $HUS^{+}D$ was 1.92 per 100,000 and 4.19 per 100,000 among those aged less than five years old. 34% of children with $HUS^{+}D$ required dialysis during the acute phase of the illness. The mortality rate was 4%. All *Streptococcus pneumoniae* associated cases required dialysis during the course of their illness.(15)

Alberta

The incidence rate of HUS in Alberta between 2000 and 2011 ranged from 0.06 – 0.38 cases per 100,000 (average of 0.20 cases per 100,000). 80 cases were reported during this period (average of 6.6 cases per year) affecting individuals from 0 – 87 years of age. The median age was 3 years and the majority of cases, 52/80 (65%), occurred in the ≤5 years of age group.



	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Cases	15	21	17	20	16	5	14	8	9	5	6	6	2	1	6	5	9	9	12	7	5	10	2	6	5	4
Rate	0.61	0.85	0.68	0.79	0.62	0.19	0.53	0.30	0.33	0.18	0.22	0.21	0.07	0.03	0.20	0.17	0.29	0.29	0.38	0.22	0.15	0.29	0.06	0.17	0.13	0.10

Source: Alberta Health Communicable Disease Reporting System (CDRS) April 24, 2012.(16)

Key Investigation

Single case/Household cluster

- Confirm the diagnosis.
- Obtain a history of illness including date of onset and signs and symptoms including any history of diarrheal illness in the recent past (e.g., usually within the previous 2 weeks).
- Determine occupation of the case. Further follow-up may be necessary depending on the causative organism. See agent-specific guidelines.
- If the case is a child, determine attendance at a childcare facility (e.g., daycare, day home) or other childcare site or school attended and grade. Further follow-up may be necessary depending on the causative organism. See agent-specific guidelines.
- Determine the initial possible source of infection taking into account the incubation period, reservoir and mode of transmission of the infectious agent. Refer to specific guidelines. Assessment may include but is not limited to (depending on the suspected infectious agent):
    - taking a detailed food history, if applicable (e.g., consumption of raw or undercooked ground beef or other possibly contaminated foods)
    - inquire about contact with animals and
    - inquire about food handling practices.

Control

Management of a Case

- Early recognition of the illness is essential to the successful management. The initial clinical presentation gives a strong indication as to the underlying cause.
- Cases should be managed according to the guidelines of the causative organism (e.g., VTEC, shigellosis, invasive pneumococcal disease) unless it is unknown, in which case further investigation may be necessary. Discussion with the MOH would be appropriate.
    - NOTE: VTEC should be sought in stool from patients diagnosed with post-diarrheal HUS. However, since HUS is typically diagnosed a week or more after onset of diarrhea when the organism may not be detectable by conventional methods, the absence of VTEC in stool does not preclude the diagnosis of probable VTEC-associated HUS.(9)

Treatment

- Treatment is generally supportive care and may involve dialysis for individuals with renal failure.

Management of Contacts

- Contacts should be managed according to the guidelines of the causative organism for the case (e.g., VTEC, shigellosis, invasive pneumococcal disease).

Preventive Measures

Prevention of HUS is largely dependent on control of the spread of VTEC and steps include the following:

- Emphasizing the importance of good sanitation and personal hygiene including thorough handwashing especially after using the washroom, changing diapers, and before eating and preparing/handling foods.
- Encouraging handwashing after contact with animals or their environments (e.g., at farms, petting zoos).
- Ensuring that slaughterhouses maintain strict operations to minimize fecal contamination during slaughtering and processing.(2)
- Educating about safer food handling practices (17) , which include:
    - Cooking meats thoroughly (especially hamburger) and to the proper internal temperature.
    - Avoiding raw milk, unpasteurized dairy products, and unpasteurized juices (like fresh apple cider).
    - Washing fruits and vegetables, especially if eaten raw. Preferably, these should be peeled.
    - Washing and sanitizing work surfaces (e.g., counters, cutting boards) and equipment used for food preparation.
    - Preventing cross-contamination by avoiding contact between raw and prepared foods (using separate equipment and utensils for handling raw foods).
    - Following cooking and storage instructions for all foods.
    - Keeping foods at safe temperatures.
    - Checking “best before” dates.
    - Using safe water.
- Early diagnosis enables early supportive treatment to be initiated and public health measures to be implemented to prevent further cases.

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