Escherichia coli O157:H7, other verotoxin-producing E coli and the hemolytic uremic syndrome in childhood

In the past decade, verotoxin-producing Escherichia coli (VTEC) have emerged as important gastrointestinal pathogens for individuals of all ages, but with an increased incidence and severity of illness in young children and the elderly (1). The most frequently identified VTEC serotype, E coli O157:H7, is strongly associated with hemolytic uremic syndrome (HUS), a leading cause of acute renal failure in childhood (2-6). Because Canada has one of the highest reported rates of VTEC infection in the world, the purpose of this statement, prepared by the Infectious Diseases and Immunization Committee of the Canadian Paediatric Society, the Canadian Association of Pediatric Nephrologists and the Canadian Paediatric Kidney Disease Research Centre, is to provide recommendations for early diagnosis of VTEC in infants and children, for preventing or interrupting the spread of VTEC, and for early diagnosis and management of HUS in order to minimize the impact of VTEC.

BACKGROUND AND NOMENCLATURE

VTEC are so named because of their ability to produce one or more exotoxins (VT-1, VT-2, VT-2 variant) that have cytopathic effects on vero cells (African green monkey kidney cells). VTEC affect other cell lines as well (7-9). VT-1 is also known as shiga-like toxin because of its structural and functional similarity to the toxin produced by Shigella dysenteriae 1.

In contrast to some of the other causes of gastroenteritis, VTEC cause disease not by local invasion of the gut mucosa but by the direct action of verotoxin on certain cells. Verotoxins bind to a specific glycolipid receptor, Gb3, found on endothelial cells of blood vessels, smooth muscle cells, renal endothelial cells and red blood cells (10-12). Once bound, verotoxins inhibit intracellular protein synthesis, thereby causing cell death. Because the structure of Gb3 is identical to that of the Pk antigen in the P blood group system, it is not surprising that P blood group status appears to influence the risk of developing HUS after VTEC infection (13-14). VTEC that produce VT-2 alone or in combination with VT-1 are more commonly associated with HUS than are organisms that produce VT-1 alone (15,16).

HOW ARE E COLI O157:H7 AND OTHER VTEC INFECTIONS IDENTIFIED?

VTEC including E coli O157:H7 require special methods for detection in the laboratory. Microbiology laboratories can screen for E coli O157:H7 by inoculating stool specimens onto MacConkey medium containing sorbitol instead of lactose (17). If this screening stool culture is negative, O157:H7 and other VTEC can be identified via methods available in reference laboratories, such as detection of free fecal verotoxin, detection of verotoxin genes through polymerase chain reaction amplification (18) or serological responses to verotoxins or the lipopolysaccharide of E coli O157 (19).

Prolonged excretion of E coli O157:H7 in stools is uncommon, and the rate of recovery of E coli O157:H7 from an infected individual falls after the sixth day of illness (20,21). Therefore, stool samples should be obtained as early in the clinical illness as possible. A negative culture from a stool obtained after the sixth day of illness does not exclude the possibility of E coli O157:H7 infection. Furthermore, a negative culture for O157:H7 at any point does not exclude the possibility of infection by other VTEC serotypes.

HOW COMMON IS E COLI O157:H7 INFECTION?

In many regions of Canada, E coli O157:H7 is the second most common bacterial pathogen found in stools submitted to clinical laboratories, falling just behind Campylobacter species (22). During the warmer summer months, the prevalence increases sufficiently to move E coli O157:H7 into first place (23). E coli O157:H7 is also more common among individuals

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with blood in their stools (23,24). Data on non-O157 VTEC are sparse, but a recent study of stool specimens submitted to a children’s hospital in Seattle found non-O157 VTEC to be more common than *Yersinia* or *Shigella* species (25).

**HOW IS VTEC INFECTION ACQUIRED?**

Because cattle are frequently colonized with VTEC, foods of bovine origin are an important source of human VTEC infection (26,27). During the slaughter of cattle, intestinal VTEC can contaminate the surface of meat. These surface contaminants can then be distributed throughout the meat when it is ground, and can survive to cause human disease if cooking time and temperature are inadequate. Investigations using assays for verotoxin have shown prevalence rates for VTEC of 36.4% in retail ground beef and 10.6% in retail ground pork specimens (28,29).

Most reported epidemics of *E coli* O157:H7 gastroenteritis have occurred after ingestion of undercooked ground beef, but outbreaks have been linked to unpasteurized milk, cheese, yoghurt, cold cuts, potatoes, contaminated water and person to person spread (1,30-36). Outbreaks of HUS have also been reported after exposure to fresh apple juice and unpasteurized apple cider (37,38). Preparation of food on a surface that has been contaminated (for example, by juices from thawing meat) can increase the risk of VTEC infection.

While appropriate emphasis has been placed on food contamination as the source of *E coli* O157:H7, person to person spread has been implicated in daycare and nursing home outbreaks of *E coli* O157:H7 infection (31,34) as well as in secondary transmission in households (39). In children with sporadic HUS, recent work also suggests that acquisition of infection may be more commonly attributable to person to person spread than to direct ingestion of contaminated foods (40). Thus, once introduced into a family, closed group, or community through contaminated food or water, VTEC infection has the potential to spread widely as a result of person to person transmission.

**HOW ARE VTEC INFECTION AND HUS RECOGNIZED CLINICALLY?**

Gastrointestinal infection with *E coli* O157:H7 most commonly begins with a crampy, watery diarrhea after an incubation period of three to four days (range one to 10 days) (1). Infection may also progress to bloody diarrhea with stools containing amounts of blood ranging from streaks to grossly visible blood. The proportion of patients who go on to develop bloody diarrhea is unknown because those with nonbloody diarrhea are less likely to have stool cultures performed. In clinical series, bloody stools are observed in over 75% of patients and usually are evident one to three days after the onset of illness (41). Half the patients also have vomiting, but only about one-third develop fever. In the majority of patients, symptoms usually resolve after a week. More severe manifestations of this illness include intussusception, rectal prolapse, hemolytic anemia and HUS or thrombotic thrombocytopenic purpura (1).

HUS typically appears abruptly five to nine days after the onset of gastrointestinal symptoms but can occur as early as one to two days after diarrhea begins. HUS is recognized by the rapid development of hemolytic anemia, thrombocytopenia and evidence of acute renal injury, in conjunction with variable degrees of central nervous system dysfunction (including lethargy, seizures or coma) (42). It is now clear that HUS can also occur in a subclinical form, in which renal injury escapes recognition because the child continues to produce urine, and in an incomplete form, in which patients have hemolytic anemia or thrombocytopenia without evidence of acute renal injury (43,44).

**HOW DOES HUS DEVELOP?**

The clinical features of HUS are thought to be initiated by the direct effect of verotoxin on renal endothelial cells (45), which results in cell swelling, local intravascular coagulation with platelet aggregation, mechanical damage to red blood cells and reduction in glomerular filtration (46). Oxidative damage to red blood cells may play a role in the development of the hemolytic anemia (47).

**HOW OFTEN IS HUS RECOGNIZED FOLLOWING VTEC INFECTION?**

In Canada, HUS is relatively common, with an overall incidence of 1.44/100,000 children under 15 years of age and a peak incidence of 3.11/100,000 children under five (4). This translates into approximately 75 to 90 episodes of HUS among Canadian children each year. Eighty per cent of HUS episodes occur between April and September, corresponding to the seasonal pattern of VTEC infection in Canada (personal communication).

The risk of HUS in children brought to medical attention for *E coli* O157:H7 infection is approximately 8 to 10%. Although HUS is seen at all ages, the elderly and children younger than age five have an increased risk, as do those with a more severe gastrointestinal prodrome (48). Nonetheless, 20 to 25% of patients have no visible evidence of bloody stools in the two weeks before presenting with HUS (4).

**HOW SHOULD VTEC INFECTION BE TREATED?**

At present, treatment of VTEC infection is primarily supportive. Antimotility drugs are totally contraindicated, not only because they interfere with recognition of dehydration, but also because they may prolong the time of exposure to verotoxin and thereby increase the risk of HUS (49).

The role of antibiotics in the management of VTEC infection is unclear. A small prospective placebo controlled study to evaluate the effect of trimethoprim-sulfamethoxazole in children with proven *E coli* O157:H7 infection did not show a statistically significant effect of treatment on progression of symptoms, fecal pathogen excretion or incidence of HUS (50). However, in vitro evidence indicates that verotoxin production or release is increased after exposure to antibiotics (51), suggesting that antimicrobial therapy in vivo may not be beneficial.
**HOW IS HUS TREATED?**

If HUS is suspected, the child should be referred to a centre with a specialist skilled in the management of these patients. Although large boluses of oral or intravenous fluids are usually indicated in dehydrated children with oliguria, the same therapy for oliguric children with HUS can be disastrous because of the potential for overhydration, hyponatremia and seizures. Current treatment for the child with HUS consists of careful fluid administration during periods of oliguria or anuria, judicious blood product replacement, treatment of electrolyte disturbances, control of seizures and hypertension and, when necessary, dialysis (52). Early specialized medical care has been responsible in part for the reduction in HUS mortality from 100% in 1955 to 2.6% among Canadian children in 1986-88 (4). HUS remains a serious illness, with up to 50% of affected children in some centres receiving either peritoneal dialysis or hemodialysis and with a mean length of dialysis of 14 days. Several studies have demonstrated long term morbidity following HUS, including progressive reductions in renal function in some children after discharge from hospital (53-55) and, less commonly, permanent central nervous system dysfunction ranging from mental retardation and hemiparesis to learning disabilities (56,57).

**PREVENTION**

Measures that can effectively prevent human VTEC infection have not been studied extensively. Active immunization is not yet available. Proposed methods of reducing the rate of exposure to VTEC include reducing contamination of meat in slaughterhouses and meat processing plants, and irradiating meat (58), as well as ensuring proper food storage, food preparation and cooking both at home and in the commercial food industry. An increased focus on handwashing once infection is identified within families may reduce intrafamilial transmission. To prevent further spread in daycare outbreaks, Belongia and colleagues (59) recommend that all children with *E. coli* O157:H7 gastroenteritis be excluded from daycare until two serial stool cultures obtained at least 48 h apart are negative. This strategy has not yet been compared with cohorting of infected children. Whether HUS can be prevented in patients with known VTEC infection is the subject of intensive study.

**WHY SHOULD WE ATTEMPT TO IDENTIFY THOSE WITH VTEC INFECTION?**

Early diagnosis of VTEC gastroenteritis is important in order to, first, avoid unnecessary diagnostic procedures and incorrect diagnoses in those with bloody diarrhea; second, alert the caregiver to the possibility of HUS developing; third, provide the impetus for stressing hygienic measures so that person to person transmission or further food contamination can be reduced; and fourth, report to public health officials in a timely manner so any contaminated food source can be discovered and infection control measures instituted.

**RECOMMENDATIONS**

**A) Public health:**

1. VTEC including *E. coli* O157:H7 are nationally notifiable, but early reporting to the local public health authorities must be encouraged so outbreaks can be contained.

2. Until further information is available, we recommend that children with *E. coli* O157:H7 in institutional settings or daycares be isolated or excluded until two consecutive stools are culture-negative.

3. Individuals with *E. coli* O157:H7 infection who are employed preparing food should be excluded from work until their stool cultures are negative.

**B) Laboratory:**

4. To promote identification of VTEC infection, we recommend that clinical microbiology laboratories use the MacConkey-sorbitol procedure to screen for *E. coli* O157:H7 whenever a stool specimen is cultured for bacterial pathogens.

**C) Physician:**

5. We recommend that all children with bloody diarrhea have stool specimens submitted to a microbiology laboratory that is equipped to screen for *E. coli* O157:H7.

6. We recommend that all children with nonbloody diarrhea have stool specimens screened for *E. coli* O157:H7 whenever there has been exposure to undercooked ground beef or unpasteurized milk, or close contact with an individual with suspected or documented VTEC infection.

7. Antimotility agents should not be used with suspected or proven VTEC gastroenteritis and are not recommended in any other type of gastroenteritis in children.

8. There are no data available to support the use of antibiotics in cases of VTEC gastroenteritis.

9. To improve the early detection of HUS among children with proven VTEC gastroenteritis, we recommend that physicians consider performing a urinalysis, an examination of the peripheral smear, a complete blood count and a serum creatinine assay seven to 10 days after the onset of diarrhea. If there are any abnormalities on these tests, the child should be discussed with a specialist familiar with HUS. In the case of the child in whom HUS is strongly suspected, the tests should be done immediately and, if they are abnormal, the child should be referred to a pediatrician (and preferably a pediatric nephrologist) even if VTEC infection is not yet proven.
Hamburger disease or barbecue syndrome is the common name for one type of food poisoning that is caused by a germ known as verotoxigenic Escherichia coli, E coli O157:H7, or VTEC. The germ causes illness by producing a toxin (ie, a poison) that can break down the lining of the intestines and in some cases damage the kidneys.

Where do VTEC come from?
Most outbreaks of VTEC gastroenteritis have occurred after consumption of undercooked contaminated ground beef (hamburger) but outbreaks have also been reported after consumption of unpasteurized milk, cheese or yoghurt, cold cuts, unpasteurized apple juice or cider, or water contaminated with the germ. The germ can also be spread from one infected person to another. VTEC infection is more common in the spring and summer than in the winter.

What are the symptoms?
The infected person typically has the following symptoms:
• Severe stomach cramps and bloody diarrhea occur one to eight days after consumption of contaminated food. In some cases, the diarrhea is watery without blood. Dehydration due to loss of fluid is common.
• Fever, if present, is usually mild.
• The illness usually lasts seven to 10 days.
• Most people recover without any problems but the disease can have serious effects especially in young children and the elderly. A very serious complication in young children is a type of kidney failure called hemolytic uremic syndrome (HUS).

How can the disease be treated?
• Anyone with symptoms of bloody diarrhea, severe vomiting, bad abdominal cramps or a decrease in urination during a diarrheal illness should see their doctor.
• Antidiarrheal medication should not be taken.
• The benefit of antibiotic treatment is uncertain.
• Drinking small frequent amounts of clear fluids can help prevent dehydration.

How can the disease be prevented?
To minimize the risk of infection:
• Always wash hands BEFORE handling food, AFTER handling raw meat products, AFTER changing a diaper.
• Clean and sanitize utensils and kitchen work surfaces BEFORE and AFTER use.
• NEVER prepare ‘ready to eat’ foods such as sandwiches or salads on any counter used for the preparation of raw meats UNLESS the surface has been cleaned and sanitized.
• Place ground meat on the lowest rack in the refrigerator to avoid meat juices spilling onto other food.
• When barbecuing or cooking ground meats such as hamburger, pork or chicken patties, COOK THE MEAT THOROUGHLY AT THE CENTRE. Meat and juices should be brown, not pink or red – check to make sure.
• NEVER ORDER OR ACCEPT UNDERCOOKED ground meat products in an eating establishment
• Do NOT drink unpasteurized milk, apple juice or apple cider, and do not eat unpasteurized cheese.

KEEP COLD FOOD COLD (less than 4°C) and HOT FOODS HOT (above 60°C)

Further information on safe food handling can be obtained from your local health department

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