

Enterohemorrhagic *Escherichia coli* and Other *E. coli* Causing Hemolytic Uremic Syndrome

*Verocytotoxin producing
Escherichia coli (VTEC),
Shiga toxin producing
Escherichia coli (STEC),
Escherichia coli O157:H7*

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IOWA STATE UNIVERSITY
College of Veterinary Medicine



OIE Collaborating Centre for
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Importance

Enterohemorrhagic *Escherichia coli* (EHEC) is a subset of pathogenic *E. coli* that can cause diarrhea or hemorrhagic colitis in humans. Hemorrhagic colitis occasionally progresses to hemolytic uremic syndrome (HUS), an important cause of acute renal failure in children and morbidity and mortality in adults. Enterohemorrhagic *E. coli* O157:H7 (EHEC O157:H7) has been known to cause these syndromes since the 1980s, but clinical cases and outbreaks caused by members of other EHEC serogroups are increasingly recognized. In some areas, non-O157 EHEC may account for a greater number of cases than EHEC O157:H7. In 2011, an unusual enteroaggregative *E. coli* (EAEC) with the serotype O104:H4 was responsible for a severe outbreak of hemorrhagic colitis and HUS in Europe. What all of the HUS-associated *E. coli* seem to have in common is the ability to produce verotoxins, together with the ability to bind to and colonize human intestines. Because verotoxin genes can be transmitted between bacteria, additional *E. coli* pathotypes associated with HUS could also be discovered.

Ruminants, particularly cattle and sheep, seem to be the maintenance hosts for EHEC O157:H7 and many other verotoxin-producing *E. coli*. Some, but not all, individual animals carry these organisms in the intestinal tract, and shed them in the feces. Members of other animal species are also infected occasionally. Most infected animals do not develop any clinical signs, although members of some non-O157 serogroups may cause enteric disease in young animals, and EHEC O153 has been linked to a disease that resembles HUS in rabbits. Humans acquire EHEC by direct contact with animal carriers, their feces, infected people, and contaminated soil or water, or via the ingestion of underdone meat, other animal products, contaminated vegetables and fruit, and other foods. The infectious dose for people is very low, which increases the risk of disease. Animals do not seem to be reservoirs for enteroaggregative, verotoxin-producing *E. coli*, which are probably maintained in humans, but can also be acquired in food.

Etiology

Escherichia coli is a Gram negative rod (bacillus) in the family Enterobacteriaceae. Most *E. coli* are normal commensals found in the intestinal tract. Pathogenic strains of this organism are distinguished from normal flora by their possession of virulence factors such as exotoxins. Pathogenic *E. coli* can be classified into pathotypes by their virulence factors, together with the type of disease. The six pathotypes capable of producing gastrointestinal disease in humans are enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC), diffusely adherent *E. coli* and enterohemorrhagic *E. coli* (EHEC). Some authors consider verotoxigenic *E. coli* (VTEC) to be the sixth pathotype, and EHEC to be a subset of VTEC. Most *E. coli* virulence factors are encoded on mobile elements (e.g., bacteriophages) than can move between organisms, and some organisms can have characteristics of more than one pathotype. A new category, enteroaggregative and enterohemorrhagic *E. coli* (EAHEC), was recently proposed. Other authors call these organisms "enteroaggregative, verotoxin-producing *E. coli*."

Members of at least two pathotypes, EHEC and EAHEC, are capable of causing hemorrhagic colitis and hemolytic uremic syndrome in humans. (EAEC may cause bloody diarrhea, but it does not seem to be associated with HUS.) Both EHEC and EAHEC produce one or more toxins that are variously known as verotoxins, verocytotoxins or shiga toxins. There are two major families of verotoxins, Vtx1 and Vtx2, each of which can be further divided into subtypes (Vtx1a, 1c and 1d; Vtx2a to Vtx2e). An *E. coli* may produce Vtx1, Vtx2, or both. Some toxins seem to be associated with human illness more often than others. Vtx2, and especially Vtx2a, seems to be more common than Vtx1 in people with the most severe disease complications. EHEC and EAHEC are able to colonize and adhere to the human intestine, though in different ways. Most EHEC carry virulence factors (such as the intimin gene, *eae*) that give them the ability to cause attaching and effacing (A/E) lesions on human intestinal epithelium. A/E lesions are characterized by close

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bacterial attachment to the epithelial cell membrane and the destruction of microvilli at the site of adherence. EAHEC carry different virulence factors, and adhere to human intestinal cells by aggregative adherence fimbriae. The virulence genes associated with attachment (such as *eae*) are used, together with the presence of the verotoxin, to identify EHEC and EAHEC. Many VTEC are neither EHEC nor EAHEC. For example, some VTEC carry virulence factors that allow them to adhere well to the intestines of animals but do not colonize humans efficiently.

Members of the other diarrhea-producing *E. coli* pathotypes might also be able to acquire verotoxins and cause HUS. No such organisms have yet been identified.

Note on terminology

The terminology for *E. coli* that cause HUS is currently inconsistent between sources. Some authors use the term EHEC for all VTEC that can cause hemorrhagic colitis and hemolytic uremic syndrome, while others prefer a strict definition based on the possession of specific virulence factors, and use the term "atypical EHEC" for similar organisms that cause HUS. Other groups use the term VTEC, while recognizing that only a subset of VTEC have been associated with human disease or HUS. There is also a proposal that all isolates should be labeled as VTEC, with an indication of the virulence factors involved in adhesion, instead of EHEC or EAHEC. For instance, organisms such as *E. coli* O157:H7 would be classified as AE-VTEC because they carry virulence factors for attaching and effacing lesions, and EAHEC such as O104:H4 would be considered Agg-VTEC.

Serotypes involved

E. coli are serotyped based on the O (somatic lipopolysaccharide), H (flagellar) and K (capsular) antigens. A number of serotypes are known to contain EHEC. Some well known organisms involved in human disease include *E. coli* O157:H7, *E. coli* O157:H- (also known as *E. coli* O157:NM, for "nonmotile"), and members of serogroups O26, O55, O91, O103, O111, O121 and O145. Additional serogroups that have been reported in human clinical cases are O45, O80, O104, O113, O117, O118, O128 and others. EHEC O153:H7 and O153:H- have been found in sick rabbits. Nearly all *E. coli* O157:H7 carry virulence factors associated with hemorrhagic colitis and HUS, and are considered to be EHEC; however, this is not necessarily the case for organisms in other serogroups. *E. coli* O157:H- is closely related to *E. coli* O157:H7, but it is not simply a nonmotile version of this organism; it has a distinctive combination of phenotypic and virulence features.

EAHEC O104:H4 caused a severe outbreak in Germany in 2011. There are only rare descriptions of other EAHEC. For instance, one enteroaggregative *E. coli* O86:NM was isolated from a fatal case of HUS in Japan.

Species Affected

Ruminants, especially cattle, sheep, and possibly goats, are the major reservoirs for EHEC O157:H7, but are not normally affected by this organism. It can also be found in asymptomatic bison and cervids (various deer, elk), and occasionally in other mammals including pigs, camelids, rabbits, horses, dogs, cats, zoo mammals (e.g., bears, large cats) and various free-living wild species (e.g., raccoons [*Procyon lotor*], opossums, rats), EHEC O157:H7 has sometimes been detected in the intestinal tracts of wild or domesticated birds, including, chickens, turkeys, geese, ostriches, pigeons, gulls, rooks, starlings and other species. In some instances, it is unclear whether a species acts as a maintenance host or if it is only a temporary carrier. For example, rabbits shedding EHEC O157:H7 have caused outbreaks in humans, but most infected rabbits were found near farms with infected cattle.

A large number of non-O157 EHEC can be involved in human disease, and the reservoir hosts for these organisms are incompletely understood. VTEC are common in asymptomatic cattle and other ruminants; some of the organisms that have been found include EHEC O145, O45 and O103, and VTEC O26, O113, O130 and O178. Members of serogroup O26 can also occur in other animals such as pigs, rabbits and chickens. EHEC O157:H- has been detected occasionally in cattle and other species, although initial studies suggested that this organism might not be animal-associated. Some wildlife, including cervids (deer, elk) and wild boar, have been found to carry various non-O157 EHEC, and might either act as reservoirs or acquire these organisms from domesticated animals. Domesticated rabbits appear to be reservoir hosts for EHEC O153:H- and O153:H7, and also seem to be susceptible to illness caused by these organisms.

Animals are not thought to be reservoir hosts for enteroaggregative *E. coli* including EAHEC O104:H4. However, experimentally infected cattle can shed this organism, at least transiently.

Zoonotic potential

EHEC and EAHEC are important causes of illness in people. However, many VTEC found in animals, including some organisms that have the virulence factors for EHEC, have never been linked to human clinical cases. Why some organisms regularly cause illness in people, and others are found rarely or not at all, is still uncertain.

Humans are the only known reservoir hosts for enteroaggregative *E. coli* and related species such as EAHEC O104:H4.

Geographic Distribution

EHEC O157:H7 infections occur worldwide. However, the lineages of this organism are reported to differ between regions, potentially influencing the incidence and severity of human disease.

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Non-O157 EHEC are also widely distributed. The importance of some EHEC serotypes may vary with the geographic area.

EAHEC O104:H4 caused a major outbreak in Europe, but it has also been identified on other continents including Africa and Asia.

Transmission

EHEC and EAHEC are transmitted by the fecal–oral route. EHEC can spread between animals by direct contact or via water troughs, shared feed, contaminated pastures or other environmental sources. Birds and flies are potential vectors. In one experiment, EHEC O157:H7 was transmitted in aerosols when the distance between pigs was at least 10 feet. The organism was thought to have become aerosolized during high pressure washing of pens, but normal feeding and rooting behavior may have also contributed.

Ruminants can shed EHEC O157:H7 transiently, intermittently or long-term, and animals that have stopped excreting it can be recolonized. This organism is known to colonize cattle at the terminal rectum (rectoanal junction); however, a recent study detected it along the entire length of the gastrointestinal tract and in the liver, suggesting that it might also persist at other sites such as the small intestine. Young ruminants are more likely to shed EHEC O157:H7 than adults. A small proportion of the cattle in a herd, called super-shedders, excrete much higher levels of this organism than others. Initial studies suggested that super-shedding is a characteristic of particular individuals; however, some recent studies indicate that it might be a transient event that can occur in any animal. Super-shedding has also been identified in sheep. Animals that are not normal reservoir hosts for EHEC O157:H7 may become colonized for a time after contact with ruminants. Some animals may transiently shed organisms that were ingested from the environment but did not become established in the intestinal tract.

Sources of human infection

People mainly become infected with EHEC O157:H7 by ingesting contaminated food and water, or during contact with animals (especially ruminants), feces and contaminated soil. The infectious dose for humans is estimated to be less than 100 organisms, and might be as few as 10. Foodborne outbreaks caused by EHEC O157:H7 are often associated with undercooked or unpasteurized animal products, particularly ground beef, but also other meats and sausages (e.g., roast pork, salami, venison) and unpasteurized milk and cheese. Additional outbreaks have been linked to lettuce, spinach, various sprouts and other contaminated vegetables, unpasteurized cider, nuts and even pickled vegetables. Contaminated irrigation water is an important source of EHEC O157:H7 on vegetables. This organism can attach to a variety of edible plant material, although it seems to bind more readily to some fruits and vegetables than others. Depending on the environmental

conditions, small numbers of bacteria left on washed vegetables may multiply significantly over several days. EHEC O157:H7 can be internalized in the tissues of some plants including lettuce, where it may not be susceptible to washing. Unexpected sources of EHEC, such as seafood (crab meat), raw prepackaged cookie dough and rice cakes, have also been reported. In some of these outbreaks, the organism was apparently introduced during food processing. EHEC O157:H7 can remain viable for long periods in many food products. It can survive for at least nine months in ground beef stored at -20°C (-4°F). It is relatively tolerant of acidity, and remains infectious for weeks to months in acidic foods such as mayonnaise, sausage, apple cider and cheddar at refrigeration temperatures. Salt might increase its resistance to inactivation in highly acidic foods such as pickles. It also resists drying. The epidemiology of non-O157 EHEC and EHEC O157:H- is incompletely understood. However, many of these outbreaks have also been associated with animal contact or foods (animal products or vegetables) or linked to water contaminated with feces.

EHEC are usually eliminated by municipal water treatment, but these organisms may occur in private water supplies such as wells. Swimming in contaminated water, especially lakes and streams, has been associated with some human cases. Soil contamination has caused outbreaks at campgrounds and other sites, often when the site had been grazed earlier by livestock. Reported environmental survival times for *E. coli* range from a few days to nearly a year, and can be influenced by moisture, temperature, oxygen content, biological/ microbial components, and other factors. Survival in a specific environment is difficult to predict; however, one study found that EHEC O157:H7 retained its infectivity for calves for approximately 6 months in simulated water trough sediments. Most field studies have been conducted in temperate climates, and there is little or no knowledge about the survival of these organisms in tropical regions.

Person-to-person transmission of EHEC and EAHEC can contribute to disease spread during outbreaks, via the fecal-oral route. Young children tend to shed these organisms longer than adults. Humans do not appear to be a significant reservoir for EHEC O157:H7. Most people excrete this organism for approximately 7 to 9 days; a minority can shed it for a few weeks and up to several months after the onset of symptoms. EAHEC, which is probably maintained in humans, seems to persist longer. In a large German outbreak, most people stopped shedding EAHEC O104:H4 by 1 month; however, this organism was still found for several months in the feces of some individuals, and for a year in a few people.

Disinfection

E. coli can be killed by numerous disinfectants including 1% sodium hypochlorite, 70% ethanol, phenolic or iodine-based disinfectants, glutaraldehyde and

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formaldehyde. This organism can also be inactivated by moist heat (121°C [250°F] for at least 15 min) or dry heat (160–170°C [320–338°F] for at least 1 hour). Foods such as ground beef can be made safe by cooking them to a minimum temperature of 160°F/ 71°C. Ionizing radiation or chemical treatment with various substances, such as sodium hypochlorite or acetic acid, may reduce or eliminate bacteria on produce.

Bacteria in biofilms are more difficult to destroy, and longer treatment times are usually necessary. Heat, steam and other physical means combined with disinfectants can be more effective than disinfectants alone.

Infections in Animals

Clinical Signs

A few members of some non-O157 EHEC serogroups (e.g., O26, O111, O118, O5) may cause diarrhea and other gastrointestinal signs in young (< 3-month-old) ruminants. However, older ruminants are unaffected by these organisms, and EHEC O157:H7 is normally carried in the intestinal tract without clinical signs. In experiments, the latter organism did not seem to cause disease in calves older than one week of age, although some neonatal (< 2-day-old) calves developed bloody or mucoid diarrhea, and some of these animals died. A recent outbreak of fatal meningoencephalitis and septicemia in one-month-old goats was caused by VTEC O157:H7.

EHEC O157:H7 does not appear to be an important pathogen in naturally-infected rabbits or piglets, although gnotobiotic and suckling piglets and young (5-10 day-old) rabbits are used as experimental models for human disease. Hemorrhagic or watery diarrhea occurs in the rabbits, and diarrhea and CNS signs in the piglets. However, EHEC O153:H- was linked to an outbreak of hemorrhagic diarrhea and an illness resembling HUS in domesticated rabbits. Rabbits that were experimentally infected with this organism also developed hemorrhagic diarrhea with lethargy, inappetence, dehydration and weight loss. VTEC that produce Vtx2e cause edema disease in pigs, but the adhesion factors involved in this disease (fimbrial adhesin, F18) are not the same as those causing EHEC-associated illness in humans, and Vtx2e seems to be rare in people with HUS.

Dogs that were experimentally inoculated with EHEC O157:H7 developed transient acute diarrhea with decreased appetite and vomiting, but recovered spontaneously without complications in 1-2 days. In the same experiment, dogs inoculated with an unspecified non-O157 EHEC (from a severe human clinical case) developed severe disease, with diarrhea and vomiting followed by lethargy and inappetence, dehydration and dramatic weight loss. These dogs also had neurological signs including seizures, cerebral infarction, blindness and coma, and died 5-6 days after the onset of clinical signs.

A few inconclusive reports suggest that EHEC might occasionally affect other species. EHEC O157:H7 was recently isolated from a few naturally-infected dromedaries (*Camelus dromedarius*) with hemorrhagic diarrhea, but there was no further information about the disease or its severity, or whether other causes were ruled out. An unspecified EHEC was detected in two nonhuman primates during an outbreak of diarrhea in captive cynomolgus and rhesus macaques. One animal was coinfecting with *Campylobacter*, and the other with *Helicobacter*, and enteroinvasive *E. coli* was found in other sick macaques during this outbreak.

Healthy mice and ferrets do not seem to be susceptible to EHEC; however, ferrets pretreated with antibiotics before experimental infection developed weight loss without diarrhea.

Post Mortem Lesions [Click to view images](#)

EHEC lesions in clinically affected ruminants are usually characterized by inflammation of the intestinal mucosa, and are generally limited to the large intestine. In some cases, a fibrinohemorrhagic exudate is present.

In rabbits experimentally infected with EHEC O153, the cecum and/or proximal colon were edematous and thickened, and the serosal surfaces had petechial or ecchymotic hemorrhages. Pale kidneys were also reported.

Dogs infected with EHEC O157:H7 had no significant gross lesions. In dogs inoculated with a non-O157 EHEC strain, the primary cause of death was microvascular thrombosis leading to kidney failure and multiple organ failure. This syndrome resembled HUS. In these dogs, inflammation and edema occurred in the small and large intestines. The kidneys were pale, with a few petechiae on the serosal surface. The liver was enlarged, with inflammation and necrotic lesions.

Diagnostic Tests

Carrier animals are usually detected by finding EHEC in fecal samples, which are either freshly voided or taken directly from the animal. Rectoanal mucosal swabs are useful for some purposes, but seem to detect fewer infected animals. Repeated sampling, as well as sampling more animals, increases the chance of detection. EHEC can also be found in other locations, such as hides or dust, and additional methods (e.g., liquid absorbing overshoes) have been suggested for sampling entire pens or groups of animals. Animals are not sampled routinely for EAHEC.

EHEC can be difficult to identify in animals. They are a minor population in the fecal flora, and they closely resemble commensal *E. coli* except in verotoxin production. There is no single technique that can be used to isolate all EHEC and EAHEC. Many diagnostic laboratories can identify VTEC O157:H7. Selective and differential media have been developed for this organism, based on its lack of β -glucuronidase activity and the inability of most strains to rapidly ferment sorbitol (e.g., MacConkey agar containing

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1% sorbitol [SMAC], hemorrhagic colitis agar, or commercial chromogenic agars). Because other strains of *E. coli*, as well as other bacteria, can also grow on these media, prior enrichment for *E. coli* O157 aids detection. Samples may be cultured in selective or nonselective liquid enrichment medium, or members of serogroup O157 can be concentrated on magnetic beads coated with an antibody to O157 (immunomagnetic separation [IMS]) before plating. Colonies suspected to be EHEC O157:H7 are confirmed to be *E. coli* with biochemical tests, and shown to have both the O157 somatic antigen and the H7 flagellar antigen with immunoassays or other techniques. While both verotoxin and EHEC-associated-genes must be confirmed to prove that an *E. coli* belongs to the EHEC pathotype, nearly all VTEC O157:H7 do carry these genes. Phage typing and various DNA-based methods, such as pulsed field gel electrophoresis (PFGE) or multiple-locus variable-number tandem-repeat analysis (MLVA), can subtype EHEC O157:H7 for epidemiology. These tests are generally done by reference laboratories. The techniques used to identify EHEC O157:H7 can miss atypical strains of this organism, including rare sorbitol-fermenting isolates.

The selective methods used to detect EHEC O157:H7 do not identify EHEC O157:H- or non-O157 EHEC, which are biochemically similar to other *E. coli* and do ferment sorbitol. Selective media and isolation techniques have been developed for only a few of these organisms. IMS beads are commercially available for concentrating some common EHEC serogroups including O26, O103, O111 and O145, and at least one selective medium (CT-RMAC) can be used to isolate and identify EHEC O26. Non-O157 VTEC are not necessarily EHEC or EAHEC, and must be tested for the virulence factors carried by these organisms. Because these techniques are labor-intensive and not widely available, non-O157 EHEC and EAHEC are generally detected by their verotoxin-production, and sent to a reference laboratory for further identification. Verotoxins or their genes can be identified with immunoassays, PCR or other tests such as Vero cell (or HeLa) toxicity assays.

Rapid immunological and nucleic acid-based tests that detect O and H antigens, verotoxin or various genes associated with EHEC are used with human clinical samples (see below) or food samples, but some kits validated for these purposes may lack sensitivity when testing fecal samples from animals.

Although cattle can produce antibodies to O157, serology is not used routinely in animals to diagnose infections with VTEC or EHEC.

Control

Disease reporting

Veterinarians should follow their national and/or local guidelines (if any) for screening and/or reporting EHEC, EAHEC and other organisms of concern. Some countries

have also defined specific EHEC, including both O157:H7 and some common non-O157 EHEC, as of regulatory concern in food products.

Prevention

Because EHEC are not usually significant pathogens in animals, preventive measures are mainly intended to reduce carriage for the benefit of humans. How best to accomplish this is still unclear. Identifying and targeting super-shedders has been proposed as a particularly effective means of control; however, the effects of such measures and methods to identify supershedding animals are still debated. Vaccines against EHEC O157:H7 may reduce shedding, and have received full or conditional approval in some countries including the U.S. and Canada, but are not in wide use. Other proposed interventions include the application of disinfectants (e.g., chlorhexidine), various antimicrobials or bacteriophages to the terminal rectum; the use of probiotics that would preferentially colonize the gastrointestinal tract; dietary manipulations; reductions in animal density in feedlots to decrease transmission rates; and hygiene/ management measures such as the provision of dry bedding, frequent cleaning of water troughs and the grouping of animals in the same cohorts through each stage of growth. These interventions are generally still in the research stage, although some appear promising. In addition, animals should not be allowed to graze pastures for a period after effluent that may contain EHEC has been applied.

Management practices to decrease EHEC in the environment include the storage of effluents on a cement floor for 3 months or longer before discharge, and the collection of all liquids in a trap to minimize leaching of liquid manure into groundwater. Some EHEC may remain after long-term storage. Composting manure before use as a fertilizer may reduce transmission from this source; however, the survival of the organism varies with the size and composition of the compost heap, the temperature attained, and the initial concentration of EHEC. Other biological processes (aerobic and anaerobic digestion), heat drying, and/or chemical treatments have been proposed to sanitize farm effluents before discharge into the environment. Soil treatments such as lime or solarization are also being investigated as a means to destroy these organisms more rapidly in contaminated soil.

Colonization seems to be uncommon in companion animals, and methods to eliminate EHEC from these animals have not been established. However, oral autovaccination with a heat-inactivated EHEC strain (O145:H-) stopped the shedding of this organism in a persistently infected cat.

Morbidity and Mortality

EHEC O157:H7 seems to be most common in ruminants. Surveys have found this organism in < 1% to 67% of cattle, depending on the country, type of herd

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studied, detection method and other factors, with most larger studies indicating an overall prevalence < 15%. In the E.U., VTEC O157 was detected in 0.2-2.3% of cattle between 2007 and 2011. Animals in feedlots appear more likely to shed EHEC O157:H7 than animals on pasture or dairy cattle. Young cattle are more likely to be infected than older animals, although this organism seems to be uncommon in preweaning calves. Its prevalence in sheep and goats appears to be similar or lower than in cattle. In cattle, EHEC O157:H7 infections seem to be influenced by the season, and many studies have found that this organism is more common from spring to early autumn. However, a few studies reported other patterns or did not find that shedding was seasonal. Management factors or climatic factors (e.g., warm climates) might account for these differences. Seasonality has also been reported in sheep. Information about other EHEC is more limited; however, VTEC were detected in 2-13.5 % of cattle in the E.U. between 2007 and 2011. VTEC isolation rates among cattle in individual European countries ranged from 0% to 54% in these studies. Seasonal prevalences of some EHEC serotypes may differ from that of O157:H7.

EHEC O157:H7 has been found in some herds of pigs, but it seems to be uncommon in this species. One U.S. study found a high prevalence (47%) of EHEC O157:H7 in bison, but only 2% of camelids appeared to carry this organism in a limited, opportunistic survey in the U.K. Its prevalence in deer is reported to be < 3% in some surveys. While EHEC O157:H7 has been found occasionally in dogs and cats, especially on farms, it was rarely detected in a few surveys of pets. Limited evidence also suggests that few horses or chickens are carriers, especially when they are not housed near ruminants. The prevalence might be higher in turkeys. EHEC O157:H7 has been detected in rabbits, and EHEC O153 might be relatively common in this species. In one study, 25% of Dutch belted rabbits and 9% of New Zealand white rabbits from one commercial source had EHEC O153:H- or O153:H7 in their feces. .

Morbidity in adult ruminants appears to be negligible or absent, although young animals may be affected by some serogroups. Deaths have been reported in some experimentally infected animals including some calves, dogs inoculated with a non-O157 EHEC from a human clinical case, and rabbits inoculated with EHEC O153.

Infections in Humans

Incubation Period

The incubation period for EHEC O157:H7-associated illness ranges from one to 16 days, but most infections become apparent after 3-4 days. The incubation period for EAHEC O104:H4 seems to be longer, with a median incubation period of 8-9 days.

Clinical Signs

Humans can be infected asymptotically with EHEC or EAHEC, or they may develop watery diarrhea, hemorrhagic colitis and/ or hemolytic uremic syndrome. Most symptomatic cases begin with diarrhea. Some resolve without treatment, but others progress to hemorrhagic colitis within a few days. Hemorrhagic colitis is characterized by diarrhea with profuse, visible blood, accompanied by abdominal tenderness, and in many cases, by severe abdominal cramps. Nausea, vomiting and dehydration may also be seen. Some patients have a low-grade fever; however, fever often resolves by the time hemorrhagic colitis appears, and can be absent. Many cases of hemorrhagic colitis are self-limiting and resolve in approximately a week. Complications in severe cases may include intestinal necrosis, perforation or the development of colonic strictures.

Hemolytic uremic syndrome occurs in a minority of patients with hemorrhagic colitis. This syndrome is most common in children, the elderly and those who are immunocompromised. It usually develops about a week after the diarrhea begins, when the patient is improving, but there are occasional cases without prodromal diarrhea. HUS is characterized by acute kidney injury, hemolytic anemia and thrombocytopenia. The relative importance of these signs varies. Some patients with HUS have hemolytic anemia and/or thrombocytopenia with little or no renal disease, while others have significant kidney disease but no thrombocytopenia and/or minimal hemolysis. Extrarenal signs can include CNS involvement, ranging from lethargy, irritability and seizures to paresis, stroke, cerebral edema or coma; respiratory syndromes (e.g., pleural effusion, fluid overload, adult respiratory distress syndrome); elevation of pancreatic enzymes or pancreatitis; and uncommon complications such as rhabdomyolysis, bacteremia, deep abscesses or myocardial involvement. The form of HUS usually seen in adults, particularly the elderly, is sometimes called thrombotic thrombocytopenic purpura (TTP). In TTP, there is typically less kidney damage than in children, but neurological signs are more common. Deaths occur most often in patients with serious extrarenal disease, such as severe CNS signs. Long-term renal complications of varying severity can be seen in some patients, although many or most children recover from HUS without permanent damage. There may also be residual extrarenal problems such as transient or permanent insulin-dependent diabetes mellitus, pancreatic insufficiency, or neurological defects such as poor fine-motor coordination.

In rare cases, EHEC including EHEC O157:H7 have caused urinary tract infections, with or without diarrhea and/or HUS.

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Diagnostic Tests

Because humans do not normally carry EHEC, clinical cases can be diagnosed by finding these organisms in fecal samples. Samples should be collected as soon as possible after the onset of diarrhea, as these bacteria may be cleared after a week. There is relatively little information yet about EAHEC; however, some people seem to shed EAHEC O104:H4 subclinically for a prolonged period after recovery.

The techniques to identify EHEC and EAHEC are similar to those used in animals. Many diagnostic laboratories can identify EHEC O157:H7. The U.S. Centers for Disease Control and Prevention (CDC) recommends that all samples also be tested for verotoxins and/or their genes, to determine whether they might contain non-O157 EHEC or EAHEC. Samples that test positive are generally sent to a reference laboratory for further testing.

Immunological and nucleic acid-based rapid tests that detect O and H antigens, verotoxin or various genes associated with EHEC and EAHEC can be used for presumptive diagnosis. These tests may include dipstick and membrane technologies, agglutination tests, microplate assays, colony immunoblotting, PCR, immunofluorescence and ELISAs. Fecal samples can be tested directly with some tests, but sensitivity is improved by testing cultures or enrichment broths. EHEC may occasionally lose the verotoxin by the time HUS develops. The results from rapid tests are usually confirmed by isolating the organism. Organisms confirmed to be EHEC or EAHEC can be subtyped at a reference laboratory, to aid in finding the source of an outbreak. Potential food and environmental sources may also be tested.

Serology is valuable in humans, particularly later in the course of the disease when EHEC are difficult to find. Diagnostic tests that detect antibodies to some serogroups, including EHEC O157:H7, are available. In some cases, antibodies may persist for months after infection. Cross-reactivity with other bacteria is possible.

Treatment

Treatment of EHEC- or EAHEC-associated hemorrhagic colitis is supportive, with measures such as fluids and a bland diet. Antibiotics do not seem to reduce symptoms, prevent complications or decrease shedding, and they appear to increase the risk of HUS. While the effects of specific antibiotics are still incompletely understood, current recommendations suggest that these drugs should be avoided if possible (although there may be some situations, such as complications, where this is not feasible). The use of antimotility agents in hemorrhagic colitis also seems to increase the risk for developing HUS. There are no established treatments to neutralize or remove verotoxins, although experimental treatments have been suggested or used. For instance, one report suggested that daily intestinal

lavage, combined with intravenous rehydration, may reduce the risk of HUS.

Patients with HUS may require intensive supportive care including treatment of kidney dysfunction, fluid management, treatment of arterial hypertension, and other measures such as ventilatory support if required. Additional treatments are under investigation. Patients who develop irreversible kidney failure may need a kidney transplant.

Azithromycin appeared to be useful in decolonizing patients who had recovered from illnesses caused by EAHEC O104:H4 but continued to shed this organism long-term.

Prevention

Frequent hand washing, especially before eating or preparing food, and good hygiene can decrease the risk of acquiring EHEC from animals and their environment. Hand washing facilities should be available in petting zoos and other areas where the public may contact livestock, and eating and drinking should be discouraged at these sites. To protect children and other household members, people who work with animals should keep their work clothing, including shoes, away from the main living areas and launder these items separately. Two children apparently became infected with EHEC O157:H7 after contact with bird (rook) feces, possibly via their father's soiled work shoes or contaminated overalls. After a number of outbreaks associated with camping in the U.K., the Scottish *E. coli* O157 Task Force has recommended that ruminants not be grazed on land for at least 3 weeks before camping begins.

Techniques to reduce microbial contamination during slaughter and meat processing can reduce the risks from animal products, though they are unlikely to eliminate these organisms completely. Some countries have established screening and control programs for EHEC O157:H7 and some other VTEC in meat. Meat should be cooked thoroughly to kill *E. coli*, and consumers should practice good hygiene to prevent cross-contamination via hands, cutting boards and other objects. Unpasteurized milk or other dairy products and unpasteurized juices can also contain EHEC, and are best avoided.

Livestock wastes and contaminated water should be kept away from watercourses or vegetable crops that will be eaten raw by humans. Current U.S. guidelines suggest a minimum of 120 m (400 ft) between feedlots and crops of leafy green vegetables; however, one experiment detected contamination on vegetable plots 180 m from a feedlot. The fresh produce industry may use various post-harvest measures, in addition to washing, to decrease contamination. A dilute chlorine solution may be used to reduce bacterial numbers; however, one study found that a vinegar wash (6% acetic acid) was more effective. Vegetables (including prewashed, bagged vegetables) should also be washed under running water before use.

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Under some environmental conditions, populations of bacteria in washed produce can build up again after a few days. Organisms carried internally in plant tissues are difficult to destroy except by irradiation or cooking.

Contamination of public water supplies is prevented by standard water treatment procedures. Livestock should be kept away from private water supplies. Microbiological testing can also be considered. People should try to avoid swallowing water when swimming or playing in lakes, ponds and streams.

Good hygiene, careful hand-washing and proper disposal of infectious feces can reduce person-to-person transmission. Thorough hand washing is especially important after changing diapers, after using the toilet, and before eating or preparing food. In some areas, regulations may prohibit infected children from attending daycare or school until they are no longer shedding organisms. Some authors suggest that isolating infected children from their young siblings or other young household members can significantly decrease the risk of secondary spread.

Morbidity and Mortality

Clinical cases caused by EHEC and EAHEC can occur sporadically or in outbreaks. For EHEC O157:H7, the estimated annual incidence ranges from < 0.5 to > 50 cases per 100,000 population in various countries. In many areas, the number of cases caused by non-O157 EHEC is thought to be at least as high, and sometimes higher. Young children are affected most often; however, there have been incidents, such as the 2011 EAHEC O104:H4 outbreak in Germany, where most cases occurred in adults (possibly because adults were more likely to eat the contaminated food). EHEC O157:H7 infections tend to occur during the warmer months in temperate climates, probably due to seasonal shedding patterns in animals and/or other factors such as eating undercooked meat at summer barbecues. Other EHEC do not necessarily follow the same seasonal pattern, and might peak at other times. Nursery schools are common sites of non-O157 EHEC outbreaks in some countries, and these outbreaks seem to be propagated by person-to-person transmission.

How many people are infected without clinical signs is uncertain. Various investigations have found that up to 5-9% of infections were asymptomatic, but some subclinically infected people were probably missed. In Japan, active surveillance suggests that 35% of EHEC infections may be subclinical, with the highest prevalence of these infections in healthy adults. Some developing countries have reported few or no cases of EHEC-associated HUS, although EHEC O157:H7 and other pathogenic organisms have been detected. The reasons for this are still unclear, but limited diagnosis and surveillance, competition with other microorganisms on foodstuffs, and/or cross-reactive immunity from other virulent *E. coli* have been suggested as possibilities.

What proportion of infected people develop uncomplicated diarrhea, hemorrhagic colitis and HUS is incompletely understood, but may differ between organisms. EHEC O157:H7 is widely considered to be one of the most virulent organisms, but members of other serotypes (e.g., EHEC O80:H2, EHEC O111, EAHEC O104:H4) have also caused severe outbreaks. In European surveillance, approximately twice as many patients had diarrhea as hemorrhagic colitis between 2007 and 2010; however, some cases may not have been seen by a physician, especially when they involved uncomplicated, non-bloody diarrhea. Approximately 5-10% of patients with hemorrhagic colitis are estimated to develop HUS, but higher percentages (up to 40%) have been reported in some outbreaks.

In clinical cases, the mortality rate varies with the syndrome. Hemorrhagic colitis alone is usually self-limiting, although deaths can occur. Complications and fatalities are particularly common among children, the elderly, and those who are immunosuppressed or have debilitating illnesses. EHEC-associated HUS/ TTP is estimated to be fatal in 1-10% of children and up to 50% of the elderly. In European surveillance, the case fatality rate in all reported EHEC infections was < 0.5%. In the EAHEC O104:H4 outbreak, the case fatality rate was 1.4% in all patients with clinical signs, and approximately 6% in patients with HUS/ TTP.

Internet Resources

Centers for Disease Control and Prevention (CDC).
Escherichia coli
<https://www.cdc.gov/ecoli/>

European Food Safety Authority. Scientific Opinion on VTEC-seropathotype and scientific criteria regarding pathogenicity assessment
<https://www.efsa.europa.eu/en/efsajournal/pub/3138>

Public Health Agency of Canada. Pathogen Safety Data Sheets and Risk Assessment
<http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php>

The Institute of Food Technologists
<http://www.ift.org>

The Merck Manual of Diagnosis and Therapy
<http://www.merckmanuals.com/professional>

USDA. FSIS. *Escherichia coli* O157:H7 and other Shiga toxin-producing *E. coli* (STEC)
https://www.fsis.usda.gov/wps/portal/fsis/topics/food-safety-education/get-answers/food-safety-fact-sheets/foodborne-illness-and-disease/escherichia-coli-o157h7/CT_Index

World Organization for Animal Health (OIE)
<http://www.oie.int>

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OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

<http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/>

OIE Terrestrial Animal Health Code

<http://www.oie.int/international-standard-setting/terrestrial-code/access-online/>

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