Enterohemorrhagic *Escherichia coli* Infections and the Hemolytic-Uremic Syndrome

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KEYWORDS

• *Escherichia coli* O157:H7 • *Escherichia coli* O104:H4 • Shiga toxin
• Enterohemorrhagic *Escherichia coli* • Hemolytic-uremic syndrome • Eculizumab

KEY POINTS

- Enterohemorrhagic *Escherichia coli* (EHEC) should be considered in all patients with bloody diarrhea, particularly if accompanied by severe abdominal pain. Fever, while often reported on history, is usually absent at presentation.
- Stool samples from all patients with bloody diarrhea should be tested for *E. coli* O157:H7 and for non-O157 serotypes of EHEC.
- HUS is the most severe complication of EHEC infection, and is characterized by nonimmune hemolytic anemia, thrombocytopenia, and acute kidney injury.
- Supportive care is the mainstay of therapy for EHEC infections; this includes intravenous fluid replacement and, in the case of HUS, antihypertensive medications, red blood cell transfusions, and renal replacement therapy (hemodialysis) as necessary.
- Strict adherence to proper food handling and hand hygiene measures is the best way to prevent both primary and secondary transmission of EHEC.

INTRODUCTION

Enterohemorrhagic *Escherichia coli* (EHEC; Shiga toxin/verotoxin-producing *E. coli*) is well known to the public as a potentially serious cause of infectious diarrhea based on several recent and well-publicized outbreaks associated with contaminated food sources. Whereas uncomplicated bloody diarrhea is the typical outcome of a Shiga toxin–producing *E. coli* infection, some patients progress to life-threatening

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hemolytic-uremic syndrome (HUS), defined by the triad of nonimmune hemolytic anemia, thrombocytopenia, and acute kidney injury. In the 2011 outbreak centered in Germany, 3842 people fell ill, many after consuming contaminated fenugreek sprouts, the suspected source. More than half of these individuals required hospitalization, and 855 developed HUS. Fifty-three patients died. The serotype responsible, *E. coli* O104:H4, was previously thought to be of limited pathogenic potential in humans; however, the outbreak strain was subsequently found to have acquired new virulence factors. Although *E. coli* O157:H7 remains the most common serotype isolated in North America, the outbreak in Germany illustrates both the emerging importance of non-O157 serotypes as agents of human disease and the potential for modern, large-scale methods of food production and distribution to result in widespread illness. This review addresses the pathogenesis, clinical presentation, diagnosis, and treatment of both EHEC infection and HUS, with a focus on the most commonly reported EHEC serotype (O157:H7), the serotype responsible for the most recent large outbreak (O104:H4), and the differences between the two.

EPIDEMIOLOGY

In the United States, the FoodNet (Foodborne Diseases Active Surveillance Network) system actively tracks laboratory-confirmed cases of foodborne bacterial and parasitic pathogens in multiple catchment areas encompassing 15% of the country's population.[1] Surveillance data from 2011 revealed 0.97 infections with *E. coli* O157:H7 for every 100,000 individuals. The combined incidence for non-O157 Shiga toxin–producing serotypes was only slightly higher at 1.10 per 100,000 population. Individual serotypes O157 (47%), O26 (14%), and O103 (11%) were most frequently isolated, and all occurred most often in children younger than 5 years. HUS was most common in the same age group. Although the incidence of *E. coli* O157:H7 infection has declined in recent years, that of non-O157 serotypes and postdiarrheal HUS has not. Furthermore, significant underdiagnosis of both O157:H7 and non-O157 serotypes is likely, as patients may not seek medical attention for less severe infections and even when they do, appropriate diagnostic testing may not always be performed.[2]

The reported incidence of EHEC infection in Europe before the 2011 outbreak was similar to that in the United States. In 2009, 3573 cases of Shiga toxin–producing *E. coli* were identified in the European Union, and the EHEC-related mortality rate had stabilized at 2 to 3 deaths per year.[3] The 2011 *E. coli* O104:H4 outbreak was unique, in size (3842 patients infected) and in that it preferentially affected adults (median age: 42 years) and women (68% of those infected). Although this may have been related to a particular virulence factor associated with this serotype, behavioral patterns (ie, increased likelihood of consumption of the suspected vector, fenugreek sprouts) may also have resulted in the peculiar distribution of illness.

Also atypical was the lack of a known animal reservoir for *E. coli* O104:H4. *E. coli* O157:H7 and common non-O157 EHEC serotypes reside in the gastrointestinal tracts of cattle and other ruminants (eg, deer, goats, and sheep), and can survive and proliferate in both the environment (including in the watershed of key growing regions) and foodstuffs.[4] EHEC infections in both cattle and humans follow a consistent seasonal pattern and occur much more commonly in the spring (June to September in the Northern hemisphere).[5] Because EHEC are extremely virulent, even a low infectious dose (100–1000 organisms) can result in clinically significant infection.[6,7] Recent outbreaks of EHEC have been linked to fresh produce, undercooked beef, and various types of processed, prepackaged, and even frozen foods (**Table 1**). **Table 1** also

Table 1
Selected outbreaks of enterohemorrhagic *E. coli* infections with known source

Source	Serotype	Location	Year	Number Affected	Hospital	HUS	Deaths
Frozen foods (chicken quesadillas suspected)[a,61]	O121	15 US states	2013	24	7	1	0
Raw clover sprouts[62]	O26	Chain restaurant in 11 US states	2012	29	7	0	0
Spinach and packaged leafy greens[63,64]	O157:H7	Single producer, 5 US states	2012	33	13	2	0
	O157:H7	USA and Canada	2006	205	103	31	3
Ground beef or beef sausage[25,65,66]	O157:H7	Denmark	2012	13	NR	8	NR
	O26:H11	Denmark	2007	20	NR	0	0
	O157:H7	Western USA	1993	501	151	45	3
Romaine lettuce[67,68]	O157:H7	Single farm, 10 US states	2011	58	34	3	0
	O145	Five US states	2010	31	11	3	0
Fenugreek sprouts (suspected)[69–72]	O104:H4	Germany	2011	3842	64%	855	53
		France	2011	24	8	7	NR
Unpasteurized milk, cheese, or other dairy products[73]	O157	Connecticut	2008	7	5	3	0
Ready-to-bake prepackaged cookie dough[74]	O157:H7	Single producer, 30 US states	2009	77	35	10	0
Petting zoos and close contact with farm animals[75,76]	O157	England	2009	93	27	17	NR
	O157:H7	North Carolina	2004	108	NR	15	0
Municipal or recreational (lakes, pools, and parks) water[52,77]	O157:H7	British Columbia, Canada	2004	10	6	1	0
	O157:H7	Ontario, Canada	2000	≈2300	65	27	7
Unpasteurized juice or cider[78]	O157:H7	Western USA and Canada	1996	70	25	14	1
White radish sprouts[79]	O157:H7	Japan	1996	9492	758	121	3

Abbreviation: NR, not reported.
[a] Outbreak ongoing at the time of publication.

illustrates how modern systems of food processing and distribution can result in widespread disease after contamination at a single source (whether grower, producer, or processor), and emphasizes the importance of disease recognition and reporting to a national food safety organization that can collate reports and explore potential relationships among illnesses in multiple jurisdictions.

In addition to contaminated food and water, EHEC infections have been acquired through person-to-person (household) transmission. Up to 20% of infections during *E. coli* O157:H7 outbreaks are estimated to occur via secondary transmission rather than exposure to the original contaminated source.[8] In the absence of a single identifiable source of infection, poor food handling and hygiene practices have been implicated in outbreaks associated with restaurants and day-care centers.[9,10]

PATHOGENESIS

EHEC combine the virulence features of 2 other *E. coli* pathotypes that cause diarrheal disease in humans (**Box 1**). With Shiga toxin–producing *E. coli* (STEC), they share bacteriophage-encoded Shiga toxins; and with enteropathogenic *E. coli* (EPEC), they share a chromosomally located pathogenicity island (the locus of enterocyte effacement [LEE]). The LEE encodes proteins necessary to produce an "attaching and effacing effect," whereby the bacteria attach to intestinal epithelial cells and induce loss of the microvilli on the apical surface.[11] These proteins include intimin, which brings the bacteria into close contact with the epithelial cell, and a type III secretion system (T3SS), by which bacterial proteins can be injected through the intestinal epithelial cell membrane. The regulation of these proteins is particularly well adapted to cause human disease. EHEC are able to survive exposure to gastric acid during passage through the stomach and to use the stimulus of the low pH to induce expression of intimin and T3SS, facilitating adhesion to epithelial cells and resulting in diarrhea once the bacteria reach the lower gastrointestinal (GI) tract.[12]

Box 1
Nomenclature of *E. coli* pathotypes causing intestinal infection in humans

Enteroaggregative *E. coli* (EAEC): Named for the pattern of adherence to cultured cells, EAEC may cause acute (including traveler's) or chronic (particularly in patients with human immunodeficiency virus) diarrhea

Enteroinvasive *E. coli* (EIEC): Possessing a plasmid-encoded type III secretion system that allows them to inject proteins through host cell membranes and subsequently to invade, multiply, and spread within intestinal epithelial cells, EIEC cause severe diarrhea with systemic symptoms, indistinguishable from shigellosis/bacillary dysentery

Enterotoxigenic *E. coli* (ETEC): Contracted through the ingestion of contaminated food and water, ETEC produce either or both of a heat-labile and heat-stable enterotoxin, and are a common cause of acute, watery, secretory diarrhea in children and travelers to resource-limited countries

Enteropathogenic *E. coli* (EPEC): Characterized by a unique attaching and effacing effect on intestinal epithelial cells, EPEC are spread by person-to-person transmission and are a common cause of severe diarrhea in infants in resource-limited settings

Shiga toxin–producing *E. coli* (STEC): Acquired through contaminated food or water, STEC harbor bacteriophages that encode the virulence factors Shiga-like toxins 1 and 2

Enterohemorrhagic *E. coli* (EHEC): A potentially severe cause of bloody diarrhea that may be complicated by HUS, EHEC shares characteristics of EPEC (attaching and effacing effect) and STEC (Shiga-like toxin 1 and/or 2 production)

Severe disease can result from other combinations of virulence factors. The EHEC serotype responsible for the European outbreak in 2011, *E. coli* O104:H4, is unique in that it has an enteroaggregative *E. coli* (EAEC) background (see **Box 1**). It possesses an EAEC virulence plasmid that encodes aggregative adherence fimbriae, rather than intimin and the T3SS.[13] Only 2 sporadic cases of HUS had previously been associated with this serotype, so the increased pathogenicity of the outbreak strain likely arose after acquisition of additional virulence factors. Unlike typical EAEC, the outbreak *E. coli* O104:H4 possessed a bacteriophage-encoded Shiga toxin (Stx2) and its promoter region, both similar to that found in EHEC serotypes. In addition, the outbreak strain also possessed a CTX-M-15 class extended-spectrum β-lactamase (ESBL), as well as a unique combination of enzymes known as SPATEs (Serine Protease Autotransporters of Enterobacteriaceae) that contributed to greater intestinal adherence and colonization.[14,15]

Once adhered to intestinal epithelial cells, EHEC produce and release Shiga-like toxin 1 (Stx1) and/or Shiga-like toxin 2 (Stx2). Stx2 and certain of its subtypes are most commonly associated with EHEC infections and HUS in humans, but for the purposes of this review the two are considered together. After release, the Shiga toxin is translocated across the intestinal epithelium and delivered to its receptor, globotriaosylceramide (Gb3), by circulating neutrophils.[16] Density of the Gb3 receptor mediates the susceptibility of individual vascular beds to the action of the Shiga toxin, and is particularly high in the kidneys, as well as the colon and brain.[17–19] Shiga toxin–mediated injury to the colonic microvasculature is the proposed mechanism leading to bloody diarrhea in EHEC infections, whereas toxin-mediated injury to renal endothelial cells leads to the acute kidney injury of HUS. Once bound to the Gb3 receptor and internalized, high intracellular concentrations of Shiga toxin induce cell death by modifying the ribosome and inhibiting elongation of the peptide chain, whereas lower intracellular concentrations of Shiga toxin alter gene expression and endothelial cell phenotype.[20]

Both Shiga toxin–induced mechanisms of cellular damage are apparent in the characteristic pathologic lesion of HUS, thrombotic microangiopathy (TMA). TMA is characterized by endothelial cell swelling and detachment from the basement membrane, and thrombosis of the microvasculature of the GI tract and kidneys.[21] Shiga toxin upregulates the expression of adhesion molecules (including E-selectin, intercellular cell adhesion molecule 1, and vascular cell adhesion molecule 1) on the endothelial cell surface, and facilitates the adherence and subsequent degranulation of neutrophils.[22] Neutrophil degranulation releases elastase, which can disrupt the extracellular matrix and result in endothelial cell detachment. Shiga toxins also increase cell-surface expression of P-selectin, and both induce the release and prevent cleavage of ultralarge von Willebrand factor. In doing so, the toxins promote platelet adhesion to the endothelial cell surface and subsequent thrombosis.[23,24]

Therefore, whereas diarrhea in EHEC infection occurs as a result of a direct interaction between intestinal epithelial cells and bacteria, bloody diarrhea and HUS both occur as a consequence of the actions of the Shiga toxin on the microvascular endothelial cells of the kidney and GI tract.

CLINICAL PRESENTATION

For *E. coli* O157:H7 infection, the incubation period between ingestion of bacteria and onset of diarrhea is approximately 3 days, although this can vary between 2 and 12 days.[25] Although not all patients with *E. coli* O157:H7 in the stool are symptomatic, severe abdominal cramping (often worse with defecation) and nonbloody diarrhea

typically occur during the first 1 to 3 days of illness, and may be accompanied by vomiting.[26] Fever may be present or reported in up to 50% of patients during this initial phase of illness, but has usually resolved by the time of presentation to medical care. In approximately 90% of patients, bloody diarrhea follows the initial phase of illness and prompts patients or their caregivers to seek medical attention.

Although no components of history or physical examination are sufficiently specific to replace microbiologic diagnosis, bloody diarrhea, severe abdominal pain, and absent fever are more consistent with EHEC infection than that caused by other enteric bacteria including *Salmonella*, non–Shiga toxin-producing *Shigella*, and *Campylobacter* species. If a source or suspected exposure can be documented, the incubation period tends to be slightly longer with EHEC than with other enteric bacteria, and was particularly prolonged in the *E. coli* O104:H4 outbreak. The clinical presentation, risk of complications, and outcome of infection with *E. coli* O157:H7, non-O157 EHEC serotypes, *E. coli* O104:H4, and other enteric bacteria are outlined in **Table 2**.

The most feared complication of EHEC infection is HUS, defined by the triad of nonimmune hemolytic anemia, thrombocytopenia, and acute renal injury. An elevated white blood cell count and vomiting before hospital admission have been associated with an increased likelihood of subsequent development of HUS.[27,28] HUS is distinguishable from other thrombotic microangiopathies by the presence of a diarrheal prodrome, and the absence of other precipitating factors or comorbidities (**Box 2**).

DIAGNOSTIC TESTING

Culture of loose stool specimens is the current gold-standard method for diagnosis of EHEC infections. Patients with EHEC infections are not typically bacteremic (even during HUS), so blood cultures, though potentially useful for ruling out other infectious causes in patients with fever, are rarely useful in diagnosing EHEC. In addition, even in EHEC infections complicated by HUS, Shiga toxin can be detected in blood only transiently, and hence is not a means of diagnosis.[29]

Current guidelines from the Centers for Disease Control and Prevention (CDC) in the United States recommend that all stool samples submitted with the diagnosis of acute, community-acquired diarrhea be tested for Shiga toxin–producing *E. coli*, a process that requires selective and differential culture media (Sorbitol MacConkey [SMAC] agar).[30] Unlike most of the *E. coli* strains found in the human GI tract, *E. coli* O157:H7 cannot ferment sorbitol, and therefore appears as colorless colonies on SMAC. Normal GI tract flora–associated *E. coli* and non-O157 serotypes of EHEC typically ferment both sorbitol and lactose, and therefore appear as pink colonies on the same media. Latex agglutination tests can then be used to confirm the O157 serotype of any colorless colonies.

With the increasing recognition of the clinical importance of non-O157 Shiga toxin–producing serotypes, the CDC recommends that all samples submitted for acute diarrhea be simultaneously tested for non-O157 serotypes. Non-O157 serotypes, including the *E. coli* O104:H4 outbreak strain, can be cultured on either MacConkey agar or SMAC and can be confirmed as Shiga toxin producers by enzyme immunoassay for the Shiga toxin, or by polymerase chain reaction for the Shiga toxin genes *stx1* and *stx2*. Agglutination with O-specific antisera for the most common serotypes may also be performed. Although initial nonculture detection methods are acceptable, the lack of a viable isolate for serotyping hinders clinical prognostication and epidemiologic follow-up. Testing for non-O157 serotypes is not done in all clinical laboratories, therefore isolates should be sent to the local Public Health (or reference) Laboratory for specialized testing.

Table 2
Clinical characteristics of infection for enterohemorrhagic *E. coli* versus other enteric bacteria

	E. coli O157:H7[1,55]	Non-O157 *E. coli* Serotypes[28,80,81]	*E. coli* O104:H4[47,70,71,82]	Other Enterics[a,1,83]
Median incubation (range)	3 d (2–12)	4 d	8 d (6–10)	Hours to days
History of recent travel (Central or South America, the Caribbean)	<5%	15%	Rare	8%–16%
Bloody diarrhea	>90%	60%	79% with HUS 56% with GI	Possible
Abdominal pain	Severe, common	Common	>90%	30%–50%
Vomiting	Common early in illness			
Documented fever at presentation	Rare	Rar	Rare	50%–70%
Stool leukocytes	50%	36%	Not reported	Common
Need for hospitalization	43%	18%	≈64%	15%–30%
HUS				
Incidence	10%–15%	<10%	22%	0%
Diarrheal prodrome	7 d (5–13)	6 d	5 d	0%
Neurologic complications[b]	Common	Common	48% of adults 26% of children	0%
Case fatality rate	<1% GI <5% HUS	<0.5% GI <5% HUS	0.6% GI 4.1% HUS	<0.5%

[a] Non–Shiga toxin-producing *Campylobacter*, *Salmonella*, or *Shigella* species.
[b] Neurologic complications include cognitive impairment, aphasia, or seizures.

Box 2
Differential diagnosis of thrombotic microangiopathy

- Hemolytic-uremic syndrome
- Thrombotic thrombocytopenic purpura (congenital or idiopathic)
- Antiphospholipid antibody syndrome
- Disseminated intravascular coagulation
- Malignant hypertension
- Scleroderma renal crisis
- Drug-induced (eg, calcineurin inhibitors)

At present, there is no diagnostic test to predict which patients, from among all those with EHEC infection, will develop HUS. However, evidence of early vascular injury can be detected even in the pre-HUS stage. Children with EHEC infection who will eventually develop HUS (but have yet to do so) have levels of prothrombotic factors and endothelial-active cytokines that are significantly higher than those in children with uncomplicated EHEC infection.[31,32] By contrast, serum levels of angiopoietin-1, a key mediator of endothelial cell quiescence, decline with progressive stages of complicated *E. coli* O157:H7 infection, and can partially discriminate between those children who will have an uncomplicated course of EHEC infection and those who will develop HUS.[33] Although none of these markers are sufficiently specific to be used as the sole predictors of progression to HUS, combinations of markers may ultimately aid clinicians in prognostication.

MANAGEMENT

For EHEC-associated gastroenteritis, supportive care and intravenous fluid replacement are the cornerstones of therapy. Judicious administration of intravenous fluid and sodium early in illness in children with bloody diarrhea appears to improve outcomes in the subgroup which eventually develops HUS.[34] Antimotility agents and, possibly, other drugs with antimotility effects (such as narcotics) should not be administered, as these have been associated with an increased risk of development of HUS in some, but not all, studies.[28,35] Nonsteroidal anti-inflammatory drugs should also be avoided because of a theoretical risk of worsening of gastrointestinal bleeding and/or acute kidney injury.

Perhaps the most contentious issue in the therapy for EHEC-associated gastroenteritis is the use of antibiotics. Many studies have reported a strong association between receipt of antibiotics and the eventual development of HUS, whereas other studies and a meta-analysis found no association.[36–39] When studied in vitro certain antibiotics, particularly the quinolones and trimethoprim, can stimulate the bacterial SOS response, which in turn induces the bacteriophage that encodes the Shiga toxin, resulting in increased toxin production, cell lysis, and toxin release.[40] Because the association between antibiotic use and HUS has been most consistent in children, expert opinion generally recommends that antibiotics be avoided in children with EHEC gastroenteritis.[26]

This issue was partially readdressed during the recent *E. coli* O104:H4 outbreak. In vitro studies using the outbreak strain were inconsistent, with conflicting reports that exposure to ciprofloxacin did, or did not, induce Shiga toxin production depending on the strain used and the study conditions.[15,41,42] Exposure to azithromycin was not

found to induce Shiga toxin production in vitro, and use of azithromycin in patients who had already developed HUS was associated with a shorter duration of fecal shedding of bacteria.[43] Nonetheless, neither this nor any other study yet published has examined the impact of early antimicrobial therapy on the subsequent development of HUS in a randomized, controlled fashion. At present, therefore, routine use of antibiotics in early EHEC infection is not recommended.

As with EHEC gastroenteritis, the mainstay of therapy for HUS is supportive care. All patients with HUS should be hospitalized, with frequent monitoring of laboratory markers of disease and receipt of intravenous volume replacement, antihypertensive therapy, renal replacement therapy, and packed red blood cells when necessary. No clinical benefit has been found with therapeutic anticoagulation, administration of fresh frozen plasma or glucocorticosteroids, or the use of specific Shiga toxin binders.[44]

Although therapeutic plasma exchange (TPE; plasmapheresis) is a key treatment strategy for thrombotic thrombocytopenic purpura and atypical (diarrhea-negative, EHEC-negative) HUS, its use in EHEC-associated HUS is controversial and has not been proved effective in any randomized controlled trial.[45] Because Shiga toxin is detectable in the circulation only very early in illness, and because Shiga toxin–induced endothelial and vascular dysfunction are known to precede the development of HUS, the pathophysiologic rationale for TPE in EHEC-associated HUS is lacking. A nonrandomized retrospective registry analysis of adult patients with HUS during the *E. coli* O104:H4 outbreak found no difference in neurologic symptoms or need for dialysis at the study end point of death or hospital discharge in patients who received TPE versus best supportive care. Although mortality was higher in those receiving best supportive care, such patients were older and more often had advance directives limiting care options.[46] The vast majority of pediatric patients with *E. coli* O104:H4 were treated with best supportive care (including dialysis) only, and had favorable outcomes.[47] Consequently, most investigators are circumspect about the potential benefits of TPE in EHEC-associated HUS.[48]

Eculizumab, a humanized monoclonal antibody that binds to C5 of the complement system to prevent propagation of the complement cascade, is an established therapy for atypical (diarrhea-negative) HUS that was also used during the *E. coli* O104:H4 outbreak. The rationale for its use derived from recent evidence of complement activation in typical EHEC-induced HUS and a report of the successful use of eculizumab in 3 young children with severe EHEC-induced HUS.[49,50] In the European O104 outbreak, administration of eculizumab was at the physicians' discretion and did not affect the need for dialysis or mechanical ventilation nor the occurrence of seizures and death.[51] While data from randomized trials is awaited, current evidence does not support the use of eculizumab for the treatment of EHEC-induced HUS.

PROGNOSIS

For most patients who develop uncomplicated EHEC-associated gastroenteritis and are treated with best supportive care, the prognosis is excellent. However, recent evidence suggests that long-term sequelae are possible in the adult population. Among 1977 adult patients, 1067 of whom developed gastroenteritis after exposure to a municipal water source contaminated with *E. coli* O157:H7 and *Campylobacter* species, new-onset hypertension, a combination of microalbuminuria and impaired glomerular filtration rate (GFR), and a physician-diagnosed cardiovascular event were all more common in those who had experienced symptomatic gastrointestinal illness 8 years earlier.[52]

For children who develop EHEC-associated HUS, there appears to be a small but significant risk (<5%) of end-stage renal disease, and a higher risk of hypertension, proteinuria, or a reduced GFR (25% pooled risk). Consequently, some investigators recommend screening children at least once per year for occult renal disease after an episode of EHEC-associated HUS.[53] A recent prospective study of 226 children with HUS documented full recovery in 70% after 5 years, with proteinuria (18%), hypertension (9%), decreased GFR (7%) and/or neurologic symptoms (4%) in the remainder.[54] Of note, half of these patients demonstrated late sequelae with onset more than 1 year after the acute event, again emphasizing the need for long-term follow-up.

Death is rare in both complicated and uncomplicated EHEC infections, occurring in less than 1% of patients with EHEC-associated gastroenteritis and in less than 5% of patients with EHEC-associated HUS.[55] Mortality with either syndrome is highest in those aged 60 years and older.

PREVENTION

Primary prevention of EHEC infections involves avoidance of common sources of bacteria or elimination of the bacteria through cooking or hand washing. Unpasteurized foods should be avoided, and care should be taken during food preparation to prevent cross-contamination between uncooked meat and foods that are to be served raw.[56] Raw foods, particularly leafy greens, should be washed thoroughly before eating even if prepackaged and prewashed. Ground beef should be cooked to an internal temperature of 160°F/71°C, verified by a meat thermometer. Lake or pool water should not be swallowed while swimming, and strict hand-hygiene protocols should be followed in petting zoos and after contact with animals.

Hand hygiene for both the infected patient and close contacts is also the key element in the prevention of secondary transmission. For hospitalized patients, contact precautions that include the use of gowns, gloves, and a single-bedded room are recommended. Because stringent infection control procedures such as these are impossible in homes, some investigators have advocated admitting young children with confirmed or suspected *E. coli* O157:H7 infection to hospital to avoid secondary transmission, particularly when there is another young child in the household.[57,58]

In the European outbreak of *E. coli* O104:H4, the median duration of shedding of bacteria in the stool was estimated to be 10 to 18 days, although long-term asymptomatic shedding of 7 months' duration was also described.[59] Of note, children and patients without HUS shed for a longer median duration (>30 days), as did those who received no antibiotic therapy, indicating that prolonged vigilance and compliance with hygiene measures is likely required to prevent secondary transmission.[60] Patients with ongoing fecal shedding of EHEC should be temporarily excluded from settings with a high risk of transmission (commercial food preparation, day-care centers) in accordance with local public health guidelines.

SUMMARY

EHEC continue to cause foodborne infectious diarrhea worldwide, typically resulting from a breach of proper food handling, sanitation and water processing, or hand-hygiene procedures. Clinicians therefore need to remain vigilant and consider EHEC in the differential diagnosis of diarrhea, particularly if bloody. Appropriate laboratory testing and reporting for both O157 and non-O157 serotypes, as well as prompt initiation of infection control procedures for confirmed or suspected cases, will facilitate follow-up investigation to identify the source of infection and will help to

prevent secondary transmission. Supportive care and close monitoring for complications such as HUS are also crucial. Despite the frequency and severity of EHEC outbreaks, there are as yet no proven means to predict which patients will develop HUS, and no specific therapies to either prevent progression or treat HUS once it develops. Research in these areas will be key to improving the care of patients with EHEC infection in the years to come.

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