

120 Rotavirus and Noro- and Caliciviruses

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Rotavirus

Introduction

Rotavirus is the most common cause of severe diarrhea in infants and children of developed and developing countries worldwide. Globally, rotavirus gastroenteritis causes the death of more than half a million children younger than 5 years of age. This illness creates a disease burden to virtually all societies around the world.

Etiology

Rotaviruses are included in genus *Rotavirus*, part of the *Reoviridae* family. Negative contrast electron microscopy reveals the viral particles take on a wheel-like appearance in feces, leading to the prefix “rota.”

Rotavirus particles are large in size (1,000 Å), non-enveloped, and have three concentric layers of proteins surrounding a viral genome. The genome is comprised of 11 segments of double-stranded RNA, a characteristic that allows reassortment during natural infection to yield new strains. These segments encode six structural viral proteins (VPs) that form virus particles and six nonstructural proteins (NSPs). The NSPs are synthesized in infected cells and interact with host proteins to influence pathogenesis and the immune response to infection.

The rotavirus outer capsid shell is made of the protein VP7. Spike-like projections protrude through the capsid shell and are formed by the glycoprotein VP4. The three-layered capsid renders it stable and resistant to the acidic pH in the stomach and to the digestive enzymes in the small intestine. This eases the fecal-oral transmission and delivery of the virus into the small intestine, where rotavirus causes pathological changes in structure and function.

Rotaviruses can be classified into Groups A-E, according to antigenic groups on the major capsid antigen, VP6. Only groups A, B, and C have been shown to infect humans, with group A causing the preponderance of human rotaviral gastrointestinal disease.

Rotaviruses are further classified into G and P types based on the identification of antigens on the outer capsid proteins VP7 and VP4. Most severe infections in young children are caused by serotypes G1-4. In general, the more densely populated countries show the most complex patterns of serotype prevalence. During the last two decades, G1 infections appear to have predominated globally.

Epidemiology

Worldwide, approximately 40% of hospitalizations for diarrhea in children younger than 5 years of age are attributable to rotavirus infection. The virus is identified in the stool in 10–40% of children admitted for acute diarrhea in developing countries and 35–50% in developed countries. Over 525,000 children younger than 5 years of age die annually from rotavirus, with more than 85% of these deaths occurring in African and Asian nations. In the United States, prior to the vaccine’s introduction, rotavirus infection accounted for 400,000 doctor visits, 200,000 emergency room visits, 50,000 hospitalizations, and 20–60 deaths per year, with costs amounting to \$1 billion yearly. See [Fig. 120.1](#): Rotavirus disease burden.

Virtually all children have been infected with rotavirus by the age of 5, with various degrees of severity. It is common to have progressively less severe subsequent rotavirus infections as each causes a boost in mucosal immunity. Serious rotavirus infections occur most often in children 4–24 months of age. Neonatal infection is often asymptomatic in healthy, full-term infants, presumably due to passive immunity from transplacental and breast-milk antibodies. Adults are rarely severely affected, but roughly 20% of adult household contacts of an infected infant may develop symptomatic disease.

Rotavirus gastroenteritis has a seasonal variation pattern. In the United States and other countries with a temperate climate, infections predominate during the winter months, with annual epidemics occurring between December and June. Regional variations also exist within particular climates or countries. For example, the United States rotavirus season starts in the southwest in the fall and ends in the northeast

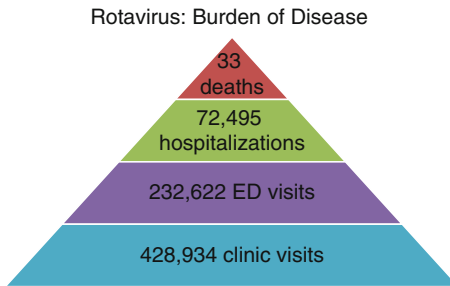


Figure 120.1
Annual rotavirus disease burden in the United States prior to vaccine introduction

in the spring. In Europe, the season begins in the southern region and spreads north over the fall to spring months. Rotavirus infections fluctuate less in the tropics, though a recent systematic review of 26 studies from tropical areas concluded that infections were more prominent in the coolest and driest months of the year.

Rotavirus is primarily transmitted person-to-person via the fecal-oral route. In developing regions, it may also be spread via fecally contaminated water. Infected individuals usually shed large quantities of virus, up to 10^{10} particles per gram of stool. As few as ten viral particles may cause infection in rotavirus-naïve patients. Viral shedding may occur up to 2 days prior to the initiation of symptoms and continues for an average of 4 days, though shedding has been reported for up to 21 days in immunocompetent patients. Immunocompromised patients may excrete the virus for even longer periods.

The virus may survive at least 4 h on hands, days to weeks on environmental surfaces, and up to weeks in drinking water. Transmission is increased in settings such as child day-care centers and family homes, where diaper changing has been identified to be the highest-risk activity. Additionally, rotavirus has been found on toys, faucets, hand-washing areas, and even food preparation areas, indicating that fomites may play a role in viral transmission. The high infectivity, presymptomatic shedding, and prolonged environmental life span are all important factors in the transmission of rotavirus.

The transmission from animals to humans is rare. There is evidence, however, that animal rotaviruses can infect humans via direct transmission of the virus or by contributing one or more RNA segments to reassortants with human strains.

The respiratory spread of rotavirus via aerosolized particles has also been suggested. Rotavirus has been detected in respiratory secretions in a small number of patients, and cases of pneumonia have been described. Rotavirus RNA

from air samples taken from rooms of hospitalized children with rotavirus gastroenteritis indicate that airborne spread may be a route of transmission of rotavirus, especially in hospital and day-care settings.

Rotavirus has its most profound effects in the gastrointestinal tract, yet systemic infection has been reported. RNA and proteins of rotavirus have frequently been detected in the blood of infected children, as well as the liver, heart, lung, and central nervous system.

Pathogenesis

Rotavirus particles are ingested orally. In the small intestine, the VP4 spikes on the capsid surface may be proteolyzed by the enzyme trypsin. This cleavage causes a conformational change in the spike structure, which then exposes other attachment sites on the surface glycoprotein. The virus is then attached to host receptors on enterocytes, and the entry process begins. The outer capsid shell is removed, and double-layered particles are inserted into the cytoplasm. These particles produce capped viral messenger RNAs (mRNAs) that are then displaced from the transcribing particles into the cell cytoplasm. There, they are then translated into proteins and replicated to new genomic RNA. This viral replication process is unique and occurs in viroplasm, electron-dense structures near the cell nucleus, and endoplasmic reticulum. Newly assembled particles with newly replicated dsRNA bud into the endoplasmic reticulum from the viroplasm and are equipped with outer capsid proteins. Fully developed virus particles are released from enterocytes via cell lysis or delivery of particles to the apical plasma membrane of cells.

Rotavirus primarily invades mature enterocyte villi, sparing the intestinal crypts. With enterocyte destruction, fluid moves into the intestinal lumen, resulting in a net loss of fluid and electrolytes in stool. Malabsorption occurs secondary to the loss of absorptive enterocytes, the decreased synthesis of lactase and other digestive enzymes, and the alteration of tight junctions between enterocytes that leads to paracellular leakage.

The rotavirus toxin, NSP4, is a nonstructural glycoprotein that may contribute to the pathophysiology by inducing a secretory component to the diarrhea. This viral enterotoxin is reported to increase intracellular calcium and activate cellular chloride channels, in turn increasing the secretion of chloride and consequently water into the lumen. NSP4 has also been found to activate the secretory reflexes of the enteric nervous system (ENS), further contributing to diarrhea.

Microischemia of villi, impaired polar transport of sucrase-isomaltase to the membrane surface, neuronally mediated intestinal hypersecretion, and altered intestinal motility are other possible mechanisms of rotavirus injury.

Pathology

Histologically, rotavirus is associated with a wide spectrum of changes, ranging from virtually normal mucosa or mild enterocyte vacuolization and loss to more significant villous blunting and crypt hyperplasia. The degree of inflammation is usually milder than that caused by other intestinal pathogens. There appears to be no direct correlation between histological findings and disease symptoms.

Clinical Manifestations

After a 2–7 day incubation period, symptoms often start abruptly with vomiting, followed by watery diarrhea. This is a noninflammatory process, with blood and white cells typically absent from the stool. In about one-third of patients, fever of over 38.9°C is reported. Other clinical features of acute rotaviral infection include anorexia and lethargy, with abdominal cramping being less common. The diarrhea can range from mild to severe, with resultant dehydration, shock, electrolyte imbalance, and even death. Severe, dehydrating rotavirus infection occurs mostly in children age 3–35 months. Rotavirus is generally a self-limited virus, with vomiting settling within 24–48 h and diarrhea in 2–7 days. Some studies have noted respiratory symptoms and otitis media in up to half of patients with rotavirus infection.

Intussusception in rotavirus infection may be caused by a disturbance in the motility of the gastrointestinal tract during an acute infection, as opposed to a typical lead point. Lipopolysaccharides may slow intestinal motility through the induction of various inflammatory agents, such as prostaglandins, cytokines, and nitric oxide.

Diagnosis

The Center for Disease Control and Prevention (CDC) defines a confirmed case of rotavirus gastroenteritis as diarrhea (3 or more loose stools within 24 h) or vomiting (1 or more episodes in a 24 h period) in a child with a positive stool detection of rotavirus by a standard assay, such as an enzyme immunoassay (EIA).

Confirmation of rotavirus infection is necessary for reliable surveillance and can be clinically useful to avoid inappropriate antimicrobial use. The most widely used method to detect rotavirus antigen in stool is EIA. These assays typically detect the rotavirus group antigen present on VP6. Many EIA kits are commercially available, providing rapid, inexpensive results with 90–100% sensitivity. Strains may be further characterized by additional enzyme immunoassay or reverse transcriptase polymerase chain reaction (RT-PCR).

Research centers use other techniques for detection and surveillance of rotavirus, including electron microscopy, RT-PCR, nucleic acid hybridization, sequence analysis, and culture. These techniques are more labor intensive and provide little additional clinical utility.

Differential Diagnosis

The non-bloody, watery diarrhea of rotavirus gastroenteritis is clinically indistinguishable from that caused by other enteric viruses, including norovirus and other caliciviruses, enteric adenovirus, and astrovirus. That said, rotavirus associated acute diarrhea may be more severe and more frequently associated with fever and vomiting. The presence of blood or leukocytes in the stool should suggest alternative diagnoses, including bacterial etiologies such as *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Escherichia coli*. Noninfectious etiologies, including intussusception, must also be considered in the infant with this presentation. Protozoal infection, particularly *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum*, should also be included in the differential diagnosis.

Prognosis

As mentioned, rotavirus infection is most frequently self-limited, with cessation of vomiting within 2 days and diarrhea within 7 days. Severe, dehydrating infection occurs more often in young children from age 3–35 months. Malnutrition is known to increase the severity of infection, with delayed small intestinal recovery and altered inflammatory responses.

Acute complications include dehydration, sodium imbalance, and possible seizures. Reye syndrome, encephalitis, rectal bleeding, and intussusception have all been associated with rotavirus, but evidence showing a causative effect is lacking.

Treatment

Rotavirus gastroenteritis is generally a self-limited illness, and treatment is largely supportive. Initial management should focus on the identification and correction of any underlying fluid and electrolyte imbalance. The assessment of dehydration and the use of oral rehydration therapy are critical and are reviewed elsewhere in this text (▶ Chap. 187, “Acute Gastroenteritis in Infants and Children”). Undernourished children are particularly at risk of severe and/or persistent symptoms, and great care must be taken to encourage early resumption of normal feeding, typically including breastfeeding. There is no role for antibiotics in the treatment of rotavirus gastroenteritis. The use of antiemetics and antidiarrheals is generally avoided. Please see ▶ Chap. 187, “Acute Gastroenteritis in Infants and Children” for further details.

The oral administration of a probiotic, *Lactobacillus GG*, is effective in both reducing viral shedding and shortening symptom duration by roughly 1 day. This improvement is most notable when the probiotic is given early in the course of the illness and seems most prominent in young children. The mechanism may be due to an enhancement of the immune response against the virus.

Orally administered Human Immune Globulin, as an investigational therapy in immunocompromised patients, was found to shorten the course of diarrhea and decrease viral excretion. Further investigation is required, and the cost-benefit ratio may not justify usage of this therapy on a wide-scale basis.

Prevention

Rotavirus attack rates are similar between developed and developing regions, suggesting that improved sanitation is unlikely to play a significant part in disease prevention. The high infectivity of the virus makes control measures difficult.

Rotaviruses are relatively resistant to chemical disinfectants used widely in hospitals. Effective agents include chlorhexidine gluconate and quaternary ammonium compounds with high alcohol content (70%). Hand washing with plain soap is often ineffective against rotavirus and may even spread the virus over a larger area of the hands. The use of a waterless, alcohol-based hand-cleaning agent before and after patient contact is recommended.

Breastfeeding plays a protective role against acquiring rotavirus. This may be due to the presence of anti-rotaviral secretory IgA and trypsin inhibitors in breast milk.

Breast-fed infants also excrete fewer viruses than formula-fed infants.

Based upon the significant morbidity and mortality of childhood rotaviral infection worldwide, great attention has been focused upon the development of a successful vaccine. Since 1983, multiple candidate vaccines have been tried. Initially, vaccines based upon the use of animal rotavirus strains that are not pathogenic in humans failed to provide sufficient clinical protection. Rotashield (Wyeth-Lederle Vaccines, Philadelphia, PA), a tetravalent simian/human reassortant rotavirus vaccine, was licensed by the FDA in 1998, based upon data showing an 80–100% protection against dehydrating rotavirus diarrhea. Within 9 months of its release, the CDC’s Vaccine Adverse Event Reporting System (VAERS) reported 15 cases of intussusception in infants who had received the vaccine. Subsequent case control and retrospective cohort studies verified a temporal association. The relative risk for intussusception within 2 weeks following the first vaccine dose exceeded 20 in both studies, prompting the vaccine’s withdrawal from the market.

Two subsequent oral rotavirus vaccines are now licensed in many nations around the world, including the United States. These vaccines have led to the decline of rotaviral infection and mortality worldwide. Rotarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium, 2006) is based on a live attenuated human rotavirus strain, G1P. RotaTeq™ (Merck & Co., Inc., Whitehouse Station, NJ, USA, 2008) is a pentavalent human–bovine reassortant, with a low rate of replication in the human gastrointestinal tract and a low rate of fecal shedding. Large phase III clinical trials have demonstrated that both Rotarix™ and RotaTeq™ are well tolerated. They have also been demonstrated to be immunogenic and highly efficacious, preventing 74–87% of all cases of rotavirus gastroenteritis and greater than 85% of those associated with severe diarrhea. In Africa and Asia, where more than 85% of rotavirus associated deaths occur, RotaTeq™ vaccination reduced cases of severe rotavirus diarrhea by greater than 50% during the first year of life when the disease burden and mortality is greatest. The World Health Organization’s Strategic Advisory Group of Experts declared that rotavirus vaccines should be included in national immunization programs worldwide, particularly in nations with high diarrheal fatalities. Diarrhea-associated deaths in these developing countries could be reduced by 25%.

The RotaTeq™ vaccine is recommended to be given as a three-dose series to infants between the ages of 6–32 weeks. The Rotarix™ vaccine is recommended to be administered as a two-dose series at the ages of 2–4 months. Details of the vaccine schedules are provided in

■ **Table 120.1**

Rotavirus vaccine schedule per the Advisory Committee on Immunization Practices (ACIP) recommendations, 2009

	2 Months	4 Months	6 Months
Rotarix® (RV1)	Rotarix® #1	Rotarix® #2	NA
	*Minimum age 6 weeks, maximum age 14 weeks 6 days	*Minimum 4 weeks between doses; Not to be given after 8 months of age	
RotaTeq® (RV5)	RotaTeq® #1	RotaTeq® #2	RotaTeq® #3
	*Minimum age 6 weeks, maximum age 14 weeks 6 days	*Minimum 4 weeks between doses #1 and #2	*Minimum 4 weeks between doses #2 and #3; Not to be given after 8 months of age

◆ **Table 120.1.** Contraindications to the rotavirus vaccine include a previous severe life-threatening allergic reaction to any components of the vaccine and some immunocompromised states.

Data from the CDC's VAERS has shown that the observed rate of intussusception in RotaTeq™-vaccinated children is not higher than the age-adjusted background rate of intussusception. Similarly, studies show no increased risk of Kawasaki syndrome with the administration of RotaTeq™ vaccine.

Since the introduction of these vaccines in 2006, the incidence of rotavirus diarrhea in infants has dramatically decreased. One study noted that from 1986 to 2006, nearly 20% of hospitalized gastroenteritis patients younger than 5 years of age tested positive for rotavirus in the stool. In the three seasons after vaccine introduction (2007–2009), the percentage dropped to 12.4%, 9.6%, and 6.4%, resulting in a decline of 66% by the study's termination. Furthermore, the rotavirus season has been found to be shortened and delayed. See ◆ **Fig. 120.2:** Hospitalizations in children due to laboratory-confirmed rotavirus gastroenteritis.

Newer approaches, such as non-replicating virus-like particle (VLP) vaccines, are presently being evaluated. Meanwhile, the current rotavirus vaccines remain a success in decreasing the morbidity and mortality from this global health disease.

Noro-Caliciviruses

Etiology

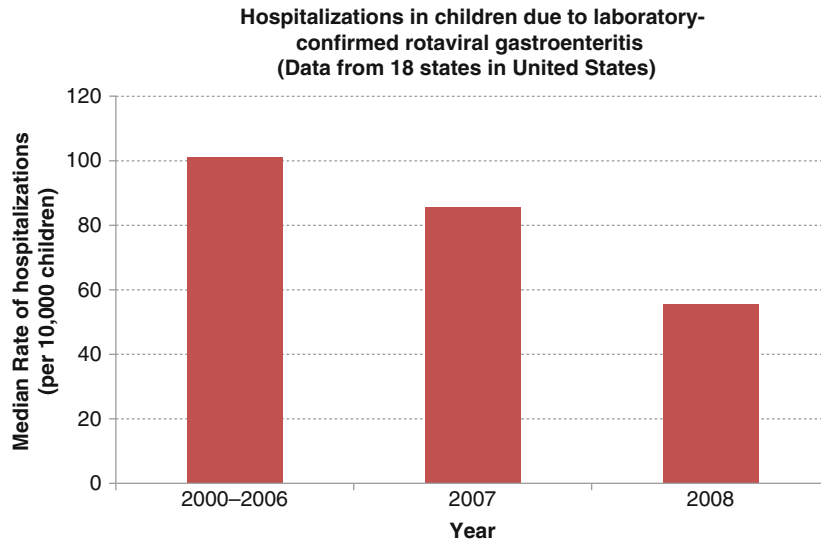
Norwalk virus carries historical import as the first confirmed viral etiology for human gastroenteritis when it was identified by electron microscopy in stools from

a severe outbreak of diarrhea in Norwalk, Ohio in 1972. Subsequently, similar appearing viruses were often called “Norwalk-like viruses.” Recent reclassifications now define the family as *Caliciviridae*, which are 20–40 nm, non-enveloped, single-stranded RNA viruses. Within this family are four distinct genera. The *Norovirus* genus accounts for roughly 95% of Calicivirus-associated gastroenteritis and is discussed here in greater detail. The other three genera (Sapovirus, Lagovirus, and Vesivirus) are less clinically relevant.

Human norovirus strains are classified into several distinct genogroups and subgroups. Genogroup II has been identified as the most common strain infecting humans worldwide. A new pandemic strain emerges every 2–4 years.

Epidemiology

Noroviruses are the most common cause of nonbacterial gastroenteritis outbreaks worldwide. Infections may occur year round, though more cases are reported during winter months. Both children and adults can be affected. The Center for Disease Control (CDC) estimates that noroviruses cause 21 million cases of gastrointestinal illness annually in the United States, accounting for half of all foodborne disease outbreaks. Norovirus infection leads to an estimated 70,000 hospitalizations and 500 deaths annually in the United States. There, only rotavirus leads to more hospitalizations for gastroenteritis in children. In developing countries, norovirus is also a common etiology for diarrhea. In India and Peru, 15% and 31%, respectively, of stool samples in hospitalized pediatric gastroenteritis patients tested positive for norovirus via PCR (◆ **Table 120.2**).



■ Figure 120.2

Hospitalizations in children due to rotavirus-confirmed gastroenteritis in 18 states of the United States, with data including pre-vaccination years 2000–2006 and 2 years following the introduction of a rotavirus vaccine

■ Table 120.2

Characteristics of rotavirus and norovirus infection

	Rotavirus	Norovirus
Genome	Non-enveloped; 11 segments of dsRNA	Non-enveloped; ssRNA
Population most affected	Children <5 years of age	Children and adults
Mode of transmission	Fecal-oral	Fecal-oral
Incubation period	2–7 days	12 h–2 days
Length of symptoms	2–7 days	< 3 days
Diagnostic testing	EIA most widely available	EIA for outbreaks
	Also RT-PCR, nucleic acid hybridization, sequence analysis, and culture	RT-PCR (limited availability)
Vaccine?	Yes; Rotateq® and Rotarix®	No

ds = double stranded

ss = single stranded

EIA = enzyme immunoassay

RT-PCR = Reverse transcriptase polymerase chain reaction

Norovirus outbreaks frequently occur in closed environments, such as cruise ships, camps, nursing homes, or schools. Typically, the outbreaks originate from direct contamination by an infected food handler. Food contaminated at its source, such as oysters from contaminated water, has also been described. As the viruses are highly contagious, outbreaks can be explosive, with potentially thousands of people being infected in a short period of time.

Norovirus is typically transmitted via the fecal-oral route or through the ingestion of contaminated food or water. Additionally, vomitus has been shown to contain infectious particles. As few as 10–100 virions are required for infection. Once exposed, roughly 30% of individuals may shed the virus prior to the onset of symptoms. Viral shedding then peaks 1–3 days after illness develops and may persist for up to 3 weeks. The virus is stable from freezing temperatures up to 60°C. All of these factors contribute to the ease of spread and the potential for large outbreaks.

Clinical Manifestations

The incubation period ranges from 12 – 48 h. Disease onset is then quite rapid, with vomiting and non-bloody, watery diarrhea. Fever occurs in roughly 40% of cases, and other constitutional symptoms such as headache, myalgias, and chills are common. In one-third of patients,

asymptomatic infection and viral shedding occur, playing a large part in viral transmission.

The illness is often mild and short-lived, with 85% of patients experiencing less than 3 days of vomiting and diarrhea. The risk for dehydration requiring hospitalization is greatest in children less than 5 years of age and in adults 65 years and older.

Pathogenesis and Pathology

In the infected host, the proximal duodenum demonstrates villous broadening and blunting, crypt-cell hyperplasia, cytoplasmic vacuolization, and inflammatory cell infiltration into the lamina propria. Histologically, the stomach and colon are spared. Intestinal brush border enzymes are diminished during acute infection, with resultant carbohydrate malabsorption. Mild steatorrhea is also noted. The prominent nausea and vomiting associated with norovirus gastroenteritis may relate to delayed gastric emptying, which has been documented in symptomatic adults.

Differential Diagnosis

The preponderance of vomiting and the high attack rate across all age groups are characteristic features of calicivirus gastroenteritis. Norovirus outbreaks can be distinguished from those caused by preformed toxins by the slightly longer incubation period (12–48 h vs. 2–6 h for toxins) and the emergence of secondary cases in household contacts. In general, calicivirus infection tends to have a milder, less dehydrating course than rotavirus. That said, the illness is not reliably clinically distinguishable from that caused by other enteric viruses, including rotavirus, enteric coronavirus, enteric adenovirus, and astrovirus.

Diagnosis

Human noroviruses cannot be cultured. Reverse transcriptase polymerase chain reaction (RT-PCR) can be used to detect viral RNA from stool or emesis samples, in addition to environmental swabs from food or water, in special circumstances. The technique is challenging as human caliciviruses are genetically diverse. Consequently, several sets of primers must be used to confirm infection. Real-time quantitative RT-PCR assays have increased both the sensitivity and specificity of this diagnostic modality.

RT-PCR detection is available in some public health and research laboratories but is not readily commercially available in most areas.

Enzyme immune assays (EIAs) for norovirus detection have been approved for commercial use in some countries, though the poor sensitivity of current assays (<50%) limits their use in sporadic cases. In outbreak situations, however, they can be used to rapidly identify norovirus as the causative agent.

In many situations, microbiologic confirmation of a suspected norovirus outbreak is not possible. The “Kaplan criteria” were developed in 1982 to distinguish outbreaks caused by norovirus from those caused by bacterial etiologies. The criteria (vomiting in greater than 50% of affected persons, a mean illness duration of 12–60 h, a mean incubation period of 24–48 h, and no bacterial pathogen identified in stool culture) are highly specific (99%) and moderately sensitive (68%) in this regard. As roughly 30% of norovirus-induced outbreaks will not satisfy all four criteria, it is still important to consider this virus in the appropriate clinical setting. Until norovirus diagnostic tests become widely available, the application of these criteria may be the most useful diagnostic aid in identifying food-borne gastroenteritis outbreaks due to norovirus.

Prognosis

As noted above, Calicivirus gastroenteritis is, in general, fairly mild and self-limited. Immunocompromised hosts, infants, and the elderly are at the highest risk for protracted illness and more severe dehydration. Reports have arisen suggesting an association of norovirus with necrotizing enterocolitis in newborns, benign seizures in infants, and inflammatory bowel disease exacerbations in pediatric patient. Further studies are required to investigate these possible links.

Treatment and Prevention

There is no specific treatment available. As with other causes of viral gastroenteritis, supportive care and attention to fluid and electrolyte balance is crucial. Please see [Chap. 187, “Acute Gastroenteritis in Infants and Children”](#) for additional details.

During an outbreak, preventing secondary spread is important in halting further progression. Enforcing personal hygiene, using contact precautions, decontaminating environmental surfaces, and using an

alcohol-based hand sanitizer have all been found to decrease the spread of infection. People with diarrhea due to norovirus refrain should refrain from the use of recreational water venues, such as pools and lakes, for at least 2 week following the resolution of symptoms.

The development of effective preventative measures is of great interest, given the significant socioeconomic burden of large, prolonged outbreaks. In contrast to rotavirus, humans do not acquire long-term immunity with norovirus infection, making vaccine development challenging. A virus-like particle vaccine is currently being evaluated.

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