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58 Viral Gastroenteritis

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Viruses are the most common cause of gastroenteritis – a syndrome of acute vomiting and diarrhea associated with inflammation of the stomach and large and small intestines. Viral gastroenteritis remains a leading cause of pediatric morbidity and mortality worldwide. With the discovery of both norovirus[1] and rotavirus[2] in the early 1970s, and subsequent improved diagnostic testing,[3] the importance of viruses as causes of diarrheal disease has been increasingly appreciated. The most important agents

TABLE 58-1. Relative Distribution of Viral Pathogens as Causes of Acute Gastroenteritis among Children under the Age of 5 Years

Agent	Hospitalizations[a] (%)	Community Disease[a] (%)
Rotaviruses	25–50	5–40
Noroviruses	5–30	10–25
Sapoviruses	<5	5–10
Astroviruses	5–10	5–10
Adenoviruses 40/41	5–12	5–10

[a](% of all viruses detected). *Other viruses often found in stool samples account for the remainder, including coronaviruses, toroviruses, picornaviruses, enteroviruses, and others.*

in children include rotaviruses, human caliciviruses (noroviruses and sapoviruses), adenovirus 40/41, and astroviruses (Table 58-1). Many other viruses (parvovirus B19, enteroviruses, coronaviruses, toroviruses, picobirnaviruses, and bocaviruses) occasionally have been associated with acute vomiting and diarrhea, but none is likely to be a common cause. Viral gastroenteritides share similar clinical presentations, modes of transmission, and treatment; many causes remain clinically undiagnosed.

ETIOLOGIC AGENTS

A small group of viruses account for most cases of acute gastroenteritis among children. These include rotaviruses, caliciviruses, astroviruses, and adenoviruses.

Rotaviruses. Rotaviruses (family Reoviridae) are 100-nm, triple-layered particles comprised of an outer capsid, inner capsid, and core.[4] The double-stranded RNA genome is composed of 11 segments which code for 6 structural proteins (VP1 to VP4, VP6, and VP7) and 6 nonstructural proteins (NSP1 to NSP6). The outer capsid is composed of 2 proteins, VP7 (G protein, for glycoprotein) and VP4 (P protein, for protease-cleaved protein). These proteins are the principal antigens to which neutralizing antibodies are directed and are the proteins that account for the classification scheme for rotavirus strains. The middle layer is made up of the VP6 protein, which is the most abundant protein in the virus and is the protein to which common immune diagnostics are directed. Rotaviruses commonly are classified according to group and serotype. Six groups of rotavirus have been described (A to F), and are based on differences in the VP6 protein. Only viruses in groups A, B, and C are known to cause disease in humans, with group A viruses being the principal cause of human disease. Groups B and C rotaviruses also cause gastroenteritis but are uncommon, and may disproportionately affect adults[5–8] (see Chapter 216, Rotaviruses). Group A rotaviruses are further classified by serotype based on their VP7 (G) and VP4 (P) proteins. While more than 10 P types and G types have each been described,[9] 5 G types (G1 to G4 and G9) and 3 P types (P[4], P[6], and P[8]) predominate globally.[9] Over 40 P–G combinations have been detected, but only 5 combinations of these common types generally account for more than 90% of circulating viruses: P[8]G1, P[4]G2, P[8]G3, P[8]G4, and P[8]G9. P[8]G1 strains are the dominant strain worldwide, accounting for 50% to 90% of seasonal strains characterized in most large reviews.[10–12] Less common strains, such as G8, G12, and G5 strains, may be of public health importance and may even predominate in any given season.[13,14]

Caliciviruses. Caliciviruses are nonenveloped, 27- to 40-nm single-stranded RNA viruses in the family Caliciviridae.[15] Human caliciviruses are divided into two genera, norovirus and sapovirus. Noroviruses include a number of genetically related viruses, of which Norwalk virus is the prototype. Noroviruses – discovered in 1972[16] – previously have been referred to by a variety of names, including "small round-structured viruses" and "Norwalk-like viruses." Likewise, sapoviruses have been referred to as "classic caliciviruses" and "Sapporo-like viruses" in reference to location of detection of the prototype strain in Japan. When viewed by electron microscopy, sapoviruses have characteristic cup-shaped depressions over the surface of the virion (Greek, *calyx* = cup), but the noroviruses, have rough, nondistinct borders and lack the *calyx* appearance (Figure 58-1). Noroviruses are further divided into five genogroups (I to V), three of which (I, II, and, rarely, IV) cause human disease. At least 8 and 19 genotypes, respectively, have been identified for genogroups I and II.[17,18] Genogroup II genotype 4 (GGII.4) viruses have been the most common cause of outbreaks in recent years; the emergence of new GGII.4 strains has been associated with a global increase in gastroenteritis outbreaks.[19,20]

Astroviruses. Astroviruses, first discovered in 1975,[21,22] are nonenveloped, single-stranded RNA viruses in the family Astroviridae. Astroviruses are 28 nm in diameter with a smooth edge, and may have a characteristic 5- or 6-pointed star-like appearance in the center (Greek, *astron* = star). Eight distinct serotypes of human astroviruses (HastV 1 to 8) have been described. Serotype 1 is detected most commonly, but more than one serotype usually circulates in communities during each season. Non-serotype 1 viruses can predominate in a season, and greater serotype diversity may be found in developing countries.[23,24]

Adenoviruses. Adenoviruses are 70- to 80-nm, nonenveloped, double-stranded DNA viruses in the family Adenoviridae.[25] While six subgenus of adenoviruses, containing at least 51 different serotypes, can cause human infection, subgenus F (serotypes 40 and 41) adenoviruses cause gastroenteritis.[26] Certain serotypes of the subgenus A and C also have been detected in acute diarrhea, but there role is likely to be minor.[27–29]

Other viruses. Other viruses are associated with gastroenteritis, including human coronaviruses and toroviruses within the virus family Coronaviridae, and picobirnavirus. Human coronaviruses and toroviruses have been detected in studies in several countries, but their association with gastroenteritis remains unclear.[30] Reports of the clinical characteristics of patients infected with the severe acute respiratory syndrome-coronavirus have described diarrhea in approximately one-fourth of cases.[31] Human bocavirus – classified in the Parvoviridae family – has been detected in diarrheal stools in children, more frequently than in control samples,[32,33] although their role in gastroenteritis has not been evaluated fully. Pestiviruses, some picornaviruses, and parvo-like viruses, reoviruses, enteroviruses, and other unclassified small round viruses have been identified in fecal specimens and implicated in sporadic cases and single outbreaks of gastroenteritis. Data are inconclusive regarding their pathogenicity.

EPIDEMIOLOGY

Two distinct epidemiologic patterns are associated with viral gastroenteritis – endemic and epidemic disease. Rotavirus, astrovirus, enteric adenovirus, and sapovirus infections occur primarily as endemic disease, while norovirus infections commonly occur both as endemic illnesses and outbreaks (Table 58-1). All common viral gastroenteritis viruses have no geographic limits. Rotavirus, astrovirus, and sapovirus infections occur in wintertime seasonal peaks in temperate countries,[24,34–37] while they often circulate year-round in tropical settings, with peaks during dry seasons.[38,39] Seasonality of adenoviruses is less distinct.[40] Noroviruses circulate year-round in most areas, but there is a clear wintertime seasonality to outbreaks in temperate locations, particularly in healthcare settings.[41,42] Rotaviruses historically had a distinct seasonal "traveling wave" of occurrence in the United States, first in the southwest, with later peaks in the northeast.[43] However, this pattern has become less evident in recent years, possibly due to demographic changes,[44] as well as the impact of vaccination. Since introduction of routine vaccination in the U.S., the rotavirus season has diminished substantially in magnitude, and also has been delayed by 2 to 4 months in some years.[45,46] In the U.S., summertime rotavirus infections are rare (with most positive test results falsely positive), but can occur among immunocompromised children.[47]

The highest rates of rotavirus infection occur in the first 2 years of life, with most hospitalizations and severe dehydrating disease

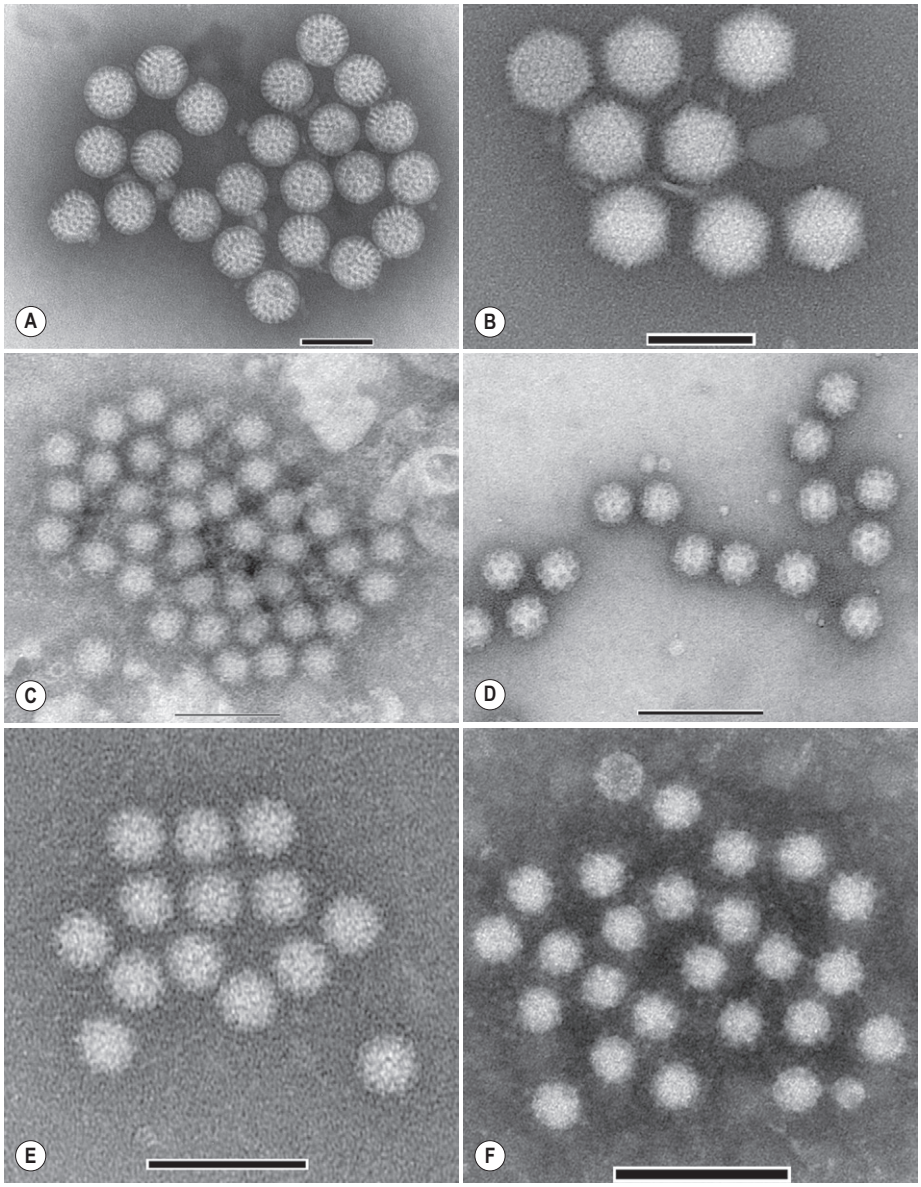

Figure 58-1. Electron micrographs of four viruses that are known to cause gastroenteritis. **(A)** Rotaviruses are 70- to 80-nm multi-shelled particles; the inner shell has a visible "wheel and spoke" character. **(B)** Adenoviruses are 70- to 90-nm icosahedral structured viruses with fiber extensions on their vertices. The fibers are fragile and not always seen on cell culture prepared adenovirus or on virus seen in fecal suspensions. **(C–E)** Noroviruses and sapoviruses are 33- to 40-nm viruses. Fecal suspension particles often are coated with gastrointestinal derived antibodies as shown in panel **C.** Human noroviruses and sapoviruses are fastidious but virus-like particles (VLPs) formed of capsid proteins can be produced in recombinant-based cultures, as shown in panels **D** and **E.** The calicivirus VLPs may be slightly larger (37 to 41 nm) than their respective viruses but have typical calicivirus structure. Panel **D** VLPs were derived from sapovirus and panel **E** from norovirus. The "star of David" image associated with caliciviruses is readily apparent on sapovirus VLPs **D** but is not visible on norovirus VLPs **E. (F)** Astroviruses are 25–30 nm, have a smooth edge, and a distinctive 5- or 6-pointed star on some particles in fecal-suspension derived virus. The smooth surface is not always present on astroviruses grown in culture and can resemble miniature versions of noroviruses. Scale bars = 100 nm. (Courtesy of Charles D. Humphrey, PhD, CDC, Atlanta, GA.)

occurring between 4 and 23 months of age.[48,49] Infections in the first 3 months are less common and often asymptomatic because of protection from maternally acquired antibodies.[48,50] Rotavirus infections can occur more than once, with each subsequent infection becoming less severe as a result of developing immunity.[48] Illness among older children and adults is less common, but can occur in people exposed to younger children in group childcare and schools. Without immunization, rotaviruses account for 25% to 50% of gastroenteritis hospitalizations among children <5 years of age and 5% to 20% of milder cases in people who seek care in clinics.[49,51] Globally, rotavirus causes approximately 450,000 deaths per year in children less than 5 years of age, with deaths among children in the poorest countries accounting for >85% of the total.[49,51b] In the U.S., rotavirus caused 55,000 to 70,000 hospitalizations annually prior to vaccine introduction,[52,53] but mortality is rare in developed countries.[54,55]

Noroviruses are now recognized as the most common cause of both endemic disease among all ages and outbreaks of gastroenteritis,[3] with an estimated 21 million illnesses a year in the U.S.[56] Norovirus may be the most common cause of pediatric gastroenteritis in the community,[57] but because disease is less severe, it is second to rotavirus as a cause of hospitalizations. Globally, norovirus is estimated to cause 12% of severe diarrheal disease in children <5 years of age.[58] In the U.S., norovirus also is the most commonly reported cause of foodborne disease while in international settings, estimates vary widely.[56,59,60] Common foods associated with outbreaks include uncooked products contaminated by ill foodhandlers who are shedding virus, and shellfish harvested from contaminated water. Healthcare facilities, including nursing homes and hospitals, are the most common settings of norovirus outbreaks, with other closed environments such as childcare facilities and cruise ships frequently affected. The emergence of new variants of norovirus (genogroup II type 4) may be associated with unusual seasonal activity and a surge in outbreaks.[19,20,61] All age groups can be infected with noroviruses, but serosurveys document that first infection is acquired at an early age.[3]

Sapoviruses most commonly are associated with sporadic gastroenteritis, usually among young children.[62,63] Sapoviruses were detected in approximately 10% of all gastroenteritis episodes in England and Finland and 4% of hospitalized cases in Finland among children <2 years of age.[64,65] Sapovirus infections tend to be less severe than norovirus;[65] outbreaks are less common and tend to occur in the elderly.[66]

Although astroviruses have been detected in all age groups, most infections are in children <2 years of age and tend to be less severe than rotavirus.[67] Serosurveys in the U.S. have shown that

>90% of children have antibody to human astroviruses by 6 to 9 years of age.[68] Disease in adults is uncommon, but can occur in outbreak settings.[69] Generally, astroviruses are detected in <10% of young children treated for gastroenteritis in outpatient clinics or in hospitals, but occasionally are found at higher frequencies.[40,70] While astroviruses primarily cause sporadic disease, outbreaks have been reported in a range of settings including nosocomial gastroenteritis in children's hospitals.[71]

Most enteric adenovirus infections occur in children <2 years of age year-round, and less often are causes of gastroenteritis among adults.[72,73] Enteric adenoviruses account for 5% to 10% of hospitalizations for acute gastroenteritis in children and may be a common cause of healthcare-associated diarrhea.[74] Enteric adenoviruses generally are detected in 1% to 4% of children with community-associated diarrhea.[75,76] Enteric adenoviruses compared with other viral agents appear to account for a smaller proportion of diarrheal disease in economically developing than in developed countries.

PATHOGENESIS

All the major enteric viruses are transmitted primarily through close person-to-person contact via the fecal–oral route.[77] Noroviruses, in addition, are spread easily through contaminated food and water, and therefore are a major cause of foodborne disease.[41,56,78] Noroviruses are present in vomitus of ill people, and droplet spread through exposure to vomitus is an efficient mechanism of spread both in healthcare and public settings, including airplanes.[79–81] The modes of transmission of adenovirus are less well understood, but transmission is presumed to be primarily through close contact by fecal–oral spread. Spread through fomites is possible for each of the agents, and may play an important role in disease acquired in institutional settings and group childcare.[82]

After oral inoculation, viruses infect mature villous enterocytes (which have both digestive and absorptive functions) of the small intestine,[83] leading to cell death, sloughing, and villus blunting. Rotavirus infection likely results in osmotic diarrhea due to loss of absorptive enterocytes. Rotavirus infections also can cause secretory diarrhea due to the opening of calcium channels, which results in an influx of calcium and efflux of sodium and water (associated with a nonstructural viral protein, NSP4).[84,85] The intraenterocyte calcium concentration also leads to cell death. In a normal host, infection resolves as the number of susceptible mature enterocytes decreases due to cell death and as the host generates an immune response. While viral gastrointestinal tract infections generally are confined to the intestine, rotavirus and norovirus infections can result in antigenemia and presence of nucleic acid in blood of ill patients,[86,87] but extraintestinal disease is rare.

Following infection, viruses are shed in large amounts in stool during the acute illness. However, rotaviruses, noroviruses, and astroviruses can be shed for 1 to 2 days prior to illness and for several days following resolution of symptoms, facilitating transmission.[77,82] Asymptomatic infection is common, especially for norovirus,[64] although the role of asymptomatic infection in transmission is unknown.

Immunity to rotavirus is acquired and multiple infections typically are required until a child is protected against disease.[48,88,89] After a primary infection, homotypic immunity is stronger, but immunity seems to broaden to other serotypes with subsequent infections.[48] Immunity to norovirus is short-lived (months to a year) and heterotypic immunity is limited, so disease occurs in older children and adults.[90] There also is a correlation between expression of histo-blood group antigens (HBGAs) and susceptibility to norovirus infection.[91–94] The expression of histo-blood group antigens (HBGAs), as determined by the *FUT2* gene, has been associated with strain-specific susceptibility to norovirus infection, and mutations in the *FUT2* gene leading to the absence of HBGA expression have been associated with resistance to infection.[91–98] However, HBGA status does not explain completely the differences among infected and uninfected people for all strains of norovirus. Because diarrheal disease caused by astrovirus, adenovirus, and sapoviruses is largely restricted to children, immunity is believed to be long-lasting.

CLINICAL MANIFESTATIONS

After a short incubation period, infections with any of the viruses lead to an acute onset of gastroenteritis (Table 58-2). Clinical characteristics of illnesses caused by the different viruses generally are indistinguishable. Vomiting often is an early sign, common in rotavirus, and particularly pronounced in norovirus infections.[99] Stools are frequent, watery, and without blood or visible mucus. Fever occurs in approximately half of children and often is an early sign. Vomiting and fever often cease within 1 to 3 days, whereas diarrhea can persist, especially in rotavirus infections. Other symptoms include abdominal cramps and malaise. Stools generally do not contain hemoglobin or fecal leukocytes.

TABLE 58-2. Epidemiologic Features of Viral Agents of Gastroenteritis

Feature	Rotavirus	Noroviruses	Sapoviruses	Astroviruses	Adenoviruses
Age of illness	<5 years	All ages	<5 years	<2 years	<2 years
Mode of transmission	Person-to-person via fecal–oral route, fomites	Person-to-person via fecal–oral route, fomites, food/water	Person-to-person via fecal–oral route	Person-to-person via fecal–oral route	Person-to-person via fecal–oral route
Incubation period	1–3 days	12–48 hours	12–48 hours	1–4 days	3–10 days
SYMPTOMS					
Diarrhea	Explosive, watery (5–10 episodes/day)	Watery with acute onset	Watery; milder than rotavirus	Watery; milder than rotavirus	Watery; milder than rotavirus; can be prolonged
Vomiting	80–90%	>50%; often dominant symptom	Less common than rotavirus	Less common than rotavirus	Less common than rotavirus
Fever	Frequent	Less common, usually mild	Less common, usually mild	Less common, usually mild	Less common, usually mild
Illness duration	2–8 days	1–5 days	1–4 days	1–5 days	3–10 days
PRINCIPAL METHODS OF CLINICAL DIAGNOSIS	Stool EIA or LPA	RT-PCR	RT-PCR	Stool EIA (not available in the United States)	Stool EIA

EIA, enzyme immunoassay; EM, electron microscopy; IEM, immune electron microscopy; LPA, latex particle agglutination; RT-PCR, reverse transcriptase-polymerase chain reaction.
Modified from Peck AJ, Bresee JS. Viral gastroenteritis. In: McMillan JA, Feigin RD, De Angelis CD, Jones MD (eds) Oski's Pediatrics, 4th ed. Philadelphia, PA, Lippincott, Williams and Wilkins, 2006, pp 1288–1294.

The most important and common complication of viral gastroenteritis is dehydration, often with electrolyte abnormalities. Malabsorption can occur during the illness and persist for weeks. Respiratory tract symptoms if present are likely due to concurrent wintertime respiratory tract viral infections. Extraintestinal complications are rare, but encephalitis, acute myositis, hemophagocytic lymphohistiocytosis, acute flaccid paralysis, and sudden infant death syndrome have been described rarely in children with rotavirus infections;[4] relationship to rotavirus infection remains unclear. Prolonged diarrhea associated with each agent has been reported among children with malnutrition and among immunocompromised people.[100] The severity and duration of norovirus gastroenteritis has been shown to be greater in vulnerable populations.[101]

Unlike in individual cases, clinical characteristics of cases in outbreak settings can predict etiology. Outbreaks that meet simple epidemiologic and clinical criteria are likely to be due to noroviruses: (1) failure to detect a bacterial or parasitic pathogen in stool specimens; (2) the occurrence of vomiting in >50% of patients; (3) mean duration of illness of 12 to 60 hours; and (4) mean incubation period of 24 to 48 hours.[99] These "Kaplan" criteria have been validated[102] widely and are used by local health departments for diagnosis of outbreaks in the absence of laboratory testing for norovirus.

DIAGNOSIS

Laboratory diagnosis of viral gastroenteritis is best made by detection of viral antigen or nucleic acid in fresh, whole stool samples obtained during the acute illness. Commercially available assays to detect rotavirus antigen in stools offer an easy and inexpensive method for diagnosis, and include enzyme immunoassay (EIA) or latex particle agglutination test for group A rotaviruses, designed to detect the VP6 protein.[4] Antigen detection tests generally have a <90% sensitivity and <95% specificity.[93] Other methods for rotavirus detection include electron microscopy, viral isolation, and polyacrylamide gel electrophoresis (PAGE) of RNA extracted directly from stool. Reverse transcriptase-polymerase chain reaction (RT-PCR) has high analytical sensitivity and can detect virus when it is not disease-causing; RT-PCR rarely is used clinically. Serologic testing for rotavirus infection is possible but impractical in clinical applications.

Commercial antigen detection kits are available for caliciviruses, but are not recommended for use in clinical settings in the U.S. because of poor sensitivity; however, testing may be useful in outbreak investigations.[103–105] RT-PCR has become the standard diagnostic assay used for caliciviruses, but seldom is used clinically. Real-time (quantitative) RT-PCR has become widely available in public health laboratories for outbreak investigations, and sequencing of the PCR product from clinical samples can permit linking cases to each other and to a common source.[106] Given the exquisite sensitivity of RT-PCR for norovirus and the high frequency of finding norovirus in healthy people,[64,107] test results must be interpreted carefully. Caliciviruses have not been propagated in cell cultures, which has hampered development of simple diagnostic tests and evaluation of disinfectants/hand sanitizers.

Commercial EIAs for detection of astrovirus antigen in stool are available in Europe, but not in the U.S.[108] RT-PCR (highly sensitive and specific), serologic assays, and electron microscopy primarily are used in research settings. Similarly, EIA and latex particle agglutination kits are available commercially and provide highly sensitive and specific antigen detection of enteric adenoviruses. All viral gastroenteritis agents are detectable by electron microscopy and immune electron microscopy, but these tests are seldom used because of relatively low sensitivity and specificity, expense, and required expertise.

TREATMENT

No specific therapies are available for viral gastroenteritis. Case management depends on accurate and rapid assessment, correction of fluid loss and electrolyte disturbances, and maintenance of adequate hydration and nutrition.[109] Oral rehydration therapy with appropriate glucose-electrolyte solutions is sufficient in most cases. Intravenous rehydration may be required for children with severe dehydration with shock or intractable vomiting. Breastfed infants should continue to nurse on demand. Infants receiving formula should continue their usual formula upon rehydration. Children taking solid foods should continue to receive their usual diet during episodes of diarrhea, although substantial amounts of foods high in simple sugars should be avoided because the osmotic content might worsen diarrhea. Use of antimicrobial agents in patients with acute gastroenteritis should be severely restricted.

Some evidence exists to support use of oral probiotics, such as *Lactobacillus* species, that reduce the duration of diarrhea caused by rotavirus.[110,111] Zinc, used both as supplement and treatment, may reduce severity, duration, and incidence of diarrhea in some populations.[112,113] Human or bovine colostrums and human serum immunoglobulin that contain antibodies to rotavirus may be beneficial in decreasing or preventing rotavirus diarrhea, but are not used routinely.

PREVENTION

Except for rotavirus, prevention of viral gastroenteritis is limited to nonspecific strategies. Breastfeeding confers some protection against rotavirus infection, and probably other viral etiologies of infections, in young infants; protection likely is mediated through antibodies and other nonimmunologic factors in human milk. Good hygiene, including hand hygiene practices, is an effective prevention strategy and should be encouraged, particularly in institutional settings, such as childcare facilities and hospitals.[114] Hand hygiene adherence in school-age children has been shown to reduce environmental contamination with norovirus.[115] Noroviruses are relatively resistant to environmental disinfection, but cleaning contaminated surfaces and food preparation areas with cleaners approved by the U.S. Environmental Protection Agency can decrease spread of viruses and likely is effective in settings where rotavirus and astrovirus outbreaks occur.[114]

Adequate reduction of transmission of viral agents of gastroenteritis is difficult because the infectious dose is low, viruses are excreted in high quantity in stool (and often vomitus) of infected people, and the agents are quite stable in the environment. Indeed, improvements in sanitation and hygiene have not reduced rates of disease from enteric viral agents to the same extent that they have reduced disease from bacterial and parasitic agents.

The best option for preventing rotavirus morbidity and mortality is use of live, oral rotavirus vaccines in routine immunization programs. Rotavirus vaccines are attenuated strains given in multiple doses designed to replace a child's initial exposures to wild-type rotavirus with strains that will not cause disease but will generate an adequate immune response to confer protection.[116] Two rotavirus vaccines are licensed. Additional vaccines are in development and may be available within the next several years. While most vaccines in clinical development are live, orally administered vaccines, parenterally administered vaccines also are being investigated.

Rotavirus vaccines are incorporated into routine immunization programs in the U.S., Australia, and several Latin American and European countries.[117,118] With introduction of vaccination, pediatric hospitalizations have declined substantially in these populations[45,119–121] and – in Mexico – a reduction in diarrhea-associated mortality has been observed.[122] Vaccine effectiveness in the field is high. Although vaccine trials show reduced efficacy (40% to 75%) in low/middle-income populations,[123–125] impact still is substantial due to the higher burden and adverse outcomes of disease. The World Health Organization has issued global recommendations for the use of rotavirus vaccines, including universal introduction in countries where diarrheal deaths account for ≥10% of mortality among children aged <5 years.[126]

Vaccines against noroviruses are in development.[127] No vaccines against other caliciviruses, astroviruses, or enteric adenoviruses are in human trials.

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