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**Introduction**

Infection of the upper gastrointestinal tract is common as the mouth is often the initial site of exposure to environmental agents. The most frequent infectious manifestation of that interaction is gastroenteritis. Gastrointestinal infections occur most commonly in infants and young children who frequently sample the environment via the oral route. Those children, with limited access to clean water, may develop severe dehydration. Though typically a mild self-limited disease in the developed world, it is responsible for up to three million deaths worldwide. In the USA, gastroenteritis is associated with over half a million outpatient visits and up to 60 deaths annually.
Definition

Gastroenteritis (GE) is a self-limited inflammatory disorder of the stomach and small intestine usually characterized by a combination of abdominal pain, diarrhea, and nausea and vomiting. Often labeled the "stomach flu," it may be caused by a host of microbes or their toxins but most commonly is due to viral infections.

Epidemiology

The epidemiology of these infections differs by age, immune status, seasonality and exposures. In the developed world, viruses are the primary pathogens accounting for 75%–90% of infectious diarrhea. Viral gastroenteritis (VGE) can be triggered by many viruses, most often noroviruses, rotavirus and enteric adenoviruses. Rotavirus, enteric adenoviruses, calicivirus, and astrovirus are most often associated with diarrheal illness in infants and young children. Norovirus GE most often occurs in explosive outbreaks amongst free-living and institutionalized adults. It may be spread person to person or via vehicles such as food or water (Table 1).

Exposure of children to these viruses is increased in daycare settings and areas with poor sanitation. They are highly infectious and transmitted via the fecal-oral route.

Winter vomiting disease was first described in 1929 (Zahorsky, 1929). Noroviruses (Norwalk-like viruses) were later identified to be the cause of this illness, named after a diarrhea outbreak amongst elementary school students in Norwalk, Ohio in 1968 (Adler and Zickl, 1969). Noroviruses (NV) were the first viral agents proven to cause GE. They are part of the Calicivirus family. Caliciviruses are single stranded, 37–41 nm, nonenveloped RNA viruses (including noroviruses 33–40 nm and sapoviruses). Because of the low inoculum needed for transmission, prolonged viral shedding and the ability to survive in the environment, Noroviruses have become major pathogens. They account for 18% of GE worldwide and are now recognized as the leading cause of foodborne illness in the United States. The CDC estimates that NV causes 19–21 million illnesses, 56,000–71,000 hospitalizations and between 570 and 800 deaths (CDC, n.d.). The GII strain of NV is the most common. Outbreaks of NV are frequently reported on cruise ships, nursing homes, schools and work places. Outbreaks most often occur in the wintertime, hence the moniker, winter vomiting disease. However, the illness does occur throughout the year, impacting older children and adults. NV GE has a short incubation period (IP) of 12–48 h, and typically causes acute onset nausea, vomiting and diarrhea which lasting under 48 h. However, viral shedding can be prolonged for weeks, even in asymptomatic persons (Robilotti et al., 2015). Some children and chronically immune suppressed persons may experience prolonged diarrhea.

Two of the most challenging NV settings are the cruise ship outbreaks which often lead to termination of the cruise and healthcare related outbreaks which commonly lead to hospital unit closures (Zingg et al., 2005). These are often difficult to control and require aggressive and frequent environmental cleaning with bleach based solutions and strict soap and water hand hygiene. NV is not inactivated by alcohol based hand sanitizers. Factors which contribute to the explosive nature of these outbreaks, include

Table 1  Epidemiologic features of viral causes of gastroenteritis

| Feature                  | Rotavirus | Noroviruses | Sapoviruses | Astroviruses | Adenoviruses |
|--------------------------|-----------|-------------|-------------|--------------|--------------|
| Predominant age of illness | <5 year   | All ages    | <5 year     | <2 year      | <2 year      |
| Mode of transmission     | Person-to-person through fecal/oral route, fomites | Person-to-person through fecal/oral and vomitus-oral, fomites, food or water | Person-to-person through fecal/oral route | Person-to-person through fecal/oral route |
| Incubation period        | 1–3 days  | 12–48 hours | 12–48 hours | 1–4 days     | 3–10 days    |
| Symptoms Diarrhea        | Explosive, watery | Watery with acute onset | Watery; milder than rotavirus | Watery; milder than rotavirus |
| Vomiting                 | 80%–90%   | >50%; often dominant symptom | Less common than rotavirus | Less common than rotavirus |
| Fever                    | Frequent  | 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    |
| Clinical diagnosis       | Stool EIA or LPA | RT-PCR     | RT-PCR      | Stool EIA (not available in United States) | Stool EIA |

EIA, enzyme immunoassay; LPA, latex particle agglutination; RT-PCR, reverse transcriptase–polymerase chain reaction.

Modified from Pack, A. J., Bresee, J. S. Viral gastroenteritis. In: McMillan, J. A., Feigin, R. D., De Angelis, C. D., Jones, M. D. Jr. (eds). Oski’s Pediatrics, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2006, pp. 1288–1294.
close contacts and restricted settings, the high infectivity of NV, NV’s environmental persistence, prolonged viral shedding and a lack of long-lived host immunity. Most of the worldwide NV outbreaks over the past decade have been associated with the emergence of the GII.4 strain of NV (Lindemith et al., 2008).

Another causative agent of VGE from the Calicivirus family of single stranded nonenveloped RNA viruses, is, Sapovirus (SV), first identified in 1976 and subsequently named after an orphanage outbreak of diarrhea in Sapporo, Japan in 1982 (Oka et al., 2015). SV can be differentiated from other GE viruses by their “Star of David” appearance on electron microscopy, however today, these are identified by molecular diagnostic testing using a reverse transcriptase-PCR assay. Similar to NV, Sapovirus outbreaks occur throughout the year, amongst all ages and are often foodborne. The clinical manifestations of SV are indistinguishable from NV.

A third and especially important cause of VGE in infants are the rotaviruses. Rotaviruses (RV) are 100 nm, nonenveloped, double stranded RNA viruses in the family Reoviridae. The genome consists of 11 segments coding for 6 structural (VP1–4, VP6 and VP7) and 6 nonstructural proteins (NSP 1–6). The virus is made up of 3 concentric shells, an outer (VP4—P protein and VP7-G protein) and inner capsid (VP6) and core. The P and G proteins define the specific serotype and induce protective neutralizing antibodies (Blacklow and Greenberg, 1991). On electron microscopy, rotavirus appears to have a well-defined central core with radiating spokes, hence the name “rota” (wheel-like) virus. RVs are classified into groups (A–F based on VP6) and serotypes based on VP7 and VP4 proteins. Group A viruses are the most common and are the only group which cause human disease. Though there are at least 15 different serotypes, most VGE is due to serotypes G1, G2, G3, G4 and G9. Rotaviruses are extremely stable in the environment and are not eliminated by hand washing.

The RV was first identified in 1973 from duodenal biopsies of children with diarrhea. They are found throughout the world and were the most common cause of severe diarrhea amongst infants and young children in the United States before the rotavirus vaccine was introduced in 2006. Prior to the rotavirus vaccine, nearly all US children were infected with rotavirus by age 5 accounting for significant morbidity: with in excess of 200,000 ER visits, 55,000–70,000 hospitalizations and 20–60 annual deaths (Rotavirus, n.d.). Worldwide, RV remains the most common VGE affecting children. The peak incidence of RV is between 3 months when maternal antibody levels of protection may wane with most infants impacted at age 2. Similar to NV, RV is shed in high concentrations in stool and is easily transmitted within households. Prior to introducing the RV vaccine in the USA, RV was seasonal, with its peak in the winter from November–April. In the vaccine era, RV GE has become more sporadic. Rotavirus infection can be asymptomatic or symptomatic with an incubation period of 1–3 days and illness lasting for 5–7 days. Though typically associated with young children, immunocompromised adults, the elderly, travelers and those caring for children with RV GE are at risk of illness.

Less common viruses associated with VGE are the astroviruses, adenoviruses and rarely coronaviruses. Astroviruses of the family Astroviridae are small, 28 nm, nonenveloped, single stranded RNA viruses which cause around 2%–10% of viral GE in children, often found in community health facilities (Bosch et al., 2014). These viruses were first identified in humans in 1975. The most prevalent of the eight serotypes is type 1. Viral GE due to these is usually mild and does not require hospitalization. They are 25–30 nm and have a five or six pointed star appearance on electron microscopy. They are identified primarily by multiplex molecular diagnostic testing of stool samples.

Human adenoviruses (HAdVs) are 70–90 nm nonenveloped double-stranded DNA viruses which cause many human illnesses but are best known for their respiratory or ocular infections. However, adenoviruses (primarily adenovirus serotypes 40, 41) cause 1.5%–5% of viral GE in children under two (Lion, 2014). Unlike RV, AdV GE does not display seasonality. Both the incubation period and illness of AdV are longer than RV or NV, (8–10 days and illness typically lasts 5–12 days). These are also most often identified using multiplex PCR diagnostic tests on stool.

Pathobiology

Despite their frequency, the pathophysiology of most of the VGE syndromes is poorly understood. All are ingested orally and target different cells within the upper gastrointestinal tract. Recent discoveries using enteroid and murine models for NV have advanced the understanding of how these viruses interact with mammalian hosts. Factors important in NV pathogenesis include: their attachment to HBGA’s, tissue and cellular tropism of the virus, the host immune response and the host gut microbiota (deGraaf et al., 2016). In murine models, NV appears to infect both enterocytes and immune cells. Infection of enterocytes has not been shown in humans. It appears that NV target human immune cells including macrophages, dendritic cells, B and T-cells. Murine NV can be transcytosed across intestinal epithelial cells in culture via microfold (M-) cells without productive infection or disruption of tight junctions (Gonzalez-Hernandez et al., 2013). These M cells are specialized intestinal epithelial cells in the gut-associated lymphoid tissue that sample particulate antigens, in the lumen of the host to deliver them to the underlying immune cells. NV exploits this pathway, to pass through the intestinal epithelium and reach their immune target cells without harming enterocytes.

H-type histo-blood group antigen (HBGAs) are glycans expressed on the surface of specific cells present in saliva and other bodily secretions and are determinants of both the ABO and Lewis blood groups. In certain cell types, α(1,3)-fucosyltransferase 2 (FUT2; also known as galactoside 2-α-1-fucosyltransferase) adds a fucose group to precursors of HBGAs, generating various HBGAs (deGraaf et al., 2016). The binding specificity of norovirus VP1 to different HBGAs varies between norovirus genotypes and is a determinant of susceptibility to specific NV strains. Nonsecretors, lacking FUT2 are less susceptible to NV infection with GI and GII strains. Commensal gut bacteria expressing HBGAs also play a role in B-cell infection by NV (Kanski, 2016). Antimicrobial treatment of the gut microbiota in mice reduces NV replication (Jones et al., 2014). Repletion of these, restores NV infectivity. In addition, the
commensal gut bacteria suppress the antiviral activity of type III interferon which allows persistence of NV within the colon (Baldridge et al., 2015). This mechanism may allow persistence and prolonged viral shedding. The mechanism for NV induced vomiting may be due to delayed emptying, from abnormal gastric motor function.

**Rotavirus Pathophysiology**

Though more is known about rotaviruses, its pathogenesis is complex and incompletely understood. The diarrhea is believed to be multifactorial due to malabsorption, the rotavirus enterotoxin and secretion triggered by activation of the enteric nervous system. RV particles are ingested, and trypsin cleaves the spike protein VP4 into two terminal fragments VP8 and VP5. The VP8 contains a hemagglutinin domain whereas the VP5 a beta-barrel domain which interact with the membranes of small intestinal enterocytes. This interaction is mediated via VP8’s interactions with sialic acid-containing and nonsialylated receptor molecules (HBGAs). RV is internalized and the outer capsid is lost, activating the virion-associated transcriptase and viral macromolecular synthases. Viral proteins and RNAs concentrate in cytoplasmic structures called viroplasms, where RNA replication and packaging take place. Intracellular events, probably involving (nonstructural protein 4) NSP4, the RV enterotoxin trigger the release of Ca$^{2+}$ from the endoplasmic reticulum (Lundgren and Svensson, 2001). The NSP4 viroporin domain is a calcium-conducting ion channel. The increase in intracellular Ca$^{2+}$ concentration begins a cascade of cellular processes, including disruption of the microvillar cytoskeletal network, lowered expression of disaccharidases and other enzymes at the apical surface, general inhibition of the Na$^+$-solute cotransport systems, and necrosis. NSP4 appears to be released specifically by a Ca$^{2+}$-dependent, nonclassical secretion pathway prior to cell lysis. These events lead to a malabsorption component of the diarrhea through reduction in absorptive capacity of the epithelium, reduced activity of Na$^+$-solute cotransporters, and reduction of digestive enzyme expression on the epithelial surface (Hagborn et al., 2012). Development of serum and mucosal antibodies against VP4 and VP7 may protect from disease. The ENS also plays a role in RV disease. Inhibition of serotonin receptors and enkephalinases may reduce the secretory component of diarrhea. Additionally, the ENS may be associated with the hypermotility and vomiting via nitric oxide pathways.

The immune response to RV involves innate, cellular and humoral immunity. An episode of asymptomatic RV may provide partial protection and reduce the likelihood of severe symptomatic infection. A single episode of rotavirus infection is inadequate to generate permanent immunity and the duration of protection is short-lived. Repeated, asymptomatic infection may help to maintain long standing immunity.

Thirty-eight percent of children are protected after the first natural episode of infection, 77% are protected from diarrhea and 87% from severe disease. Repeated exposures lead to further protection.

**Clinical Manifestations**

Viral GE is manifested by the acute onset of diarrhea often accompanied by nausea, vomiting, fever and abdominal pain. The rapid onset and vomiting may help to differentiate this from bacterial, and protozoal mediated diarrheal diseases. Viral GE is not associated with bloody diarrhea. Though certain symptom patterns may be seen more typically with specific viruses, most cannot be differentiated on the basis of symptoms alone.

**Norovirus Clinical Features**

Primarily a disease of adults, NV tends to be explosive with a short incubation period and symptoms <3 days. Nausea and vomiting are prominent early symptoms followed by watery diarrhea, cramps, headache, fever and malaise. In immunocompromised hosts the illness can be prolonged and severe with excretion of virus for months.

**Rotavirus Clinical Features**

This is primarily a disease of young children and infants. Fever which can be above 102°F Fahrenheit, vomiting and nausea preceed the onset of watery diarrhea. Unlike NV which is usually short lived, RV diarrhea can persist for 3–9 days and is the main contributor to mortality.

**Astrovirus Clinical Features**

Astroviruses may impact infants through adults, especially if immunosuppressed. Like NV its incubation is short (1–4 days) and is followed by watery diarrhea, cramps, headache, low grade fever lasting up to 5 days. Vomiting is less often seen.
Adenovirus Clinical Features

Adenovirus gastroenteritis is most often in children under 4 or immunocompromised hosts. The incubation period is more prolonged than the RNA viruses and the diarrhea may be prolonged, lasting 10–14 days.

Diagnosis

The diagnosis of VGE is often generic—that is, viral gastroenteritis. Epidemiological and clinical features may point to a specific viral etiology but samples may not be collected and identified in most settings. Clinical guidelines do not recommend diagnostic tests for most of these self-limited GE episodes (Hane et al., 2017). Before the era of rapid nucleic acid testing, diagnostic testing and differentiation was principally done for epidemiological purposes. However, stool testing should be done in those with alarm symptoms/signs (severe dehydration, renal and electrolyte dysfunction, severe abdominal pain, symptoms >1 week, age >65, immunocompromised, pregnant, bloody stools) or in outbreaks. With the widespread use of antigen and molecular diagnostics, many of these can be identified. Specific stool antigen tests are available to identify Rotavirus and Noroviruses. For rotavirus, the stool EIA antigen is widely available. Multiplex PCR testing on stool samples can rapidly identify bacterial, viral and protozoa associated with diarrheal illness.

Treatment

Medical therapy is not necessary in the majority of patients with nonsevere viral GE. The most important aspect of treatment of acute viral GE is hydration and electrolyte repletion. Oral rehydration solution (ORS) is a balanced sodium-glucose solution which has dramatically reduced the mortality of infectious diarrhea in the developing world. Diarrhea can be slowed using antidiarrheal drugs. These can either slow secretion or motility. Recent studies suggest there may be benefit to use of ondansetron to reduce upper and lower gastrointestinal symptoms in children with VGE.

Antisecretory agents such as Bismuth subsalicylate (BSS, Pepto-Bismol), and crofelemer (Mytesi, formerly Fulyzaq) may be effective for secretory diarrhea. Crofelemer is a cystic fibrosis transmembrane regulator chloride-channel blocker shown to be useful in both traveler’s diarrhea and HIV-associated diarrhea. The recommended dose of BSS is 30 mL (325 mg) of liquid or two tablets (263 mg per tablet) chewed each 30–60 min not to exceed eight doses in 24 h. Crofelemer is administered as a 125 mg delayed release tablet taken twice daily.

The two antimotility drugs used for acute diarrhea are loperamide (Imodium) and diphenoxylate/atropine (Lomotil). Loperamide, the more active of the two, works by inhibiting segmental contractions of the gut, which slows intraluminal fluid movement and allows greater absorption. Loperamide is dosed at 4 mg initially followed by 2 mg after each loose stool up to 8 mg/day in adults. Lomotil dosing is 2, 2.5 mg tabs, 3–4 times daily. Other agents used for diarrhea include adsorbents such as kaolin, pectin, charcoal, and attapulgite. These help form stools, but the number of stools and duration of diarrhea are not shortened.

Prevention

The most effective way to prevent viral GE is to wash your hands regularly for at least 20 s. This should always be done after changing diapers, using the bathroom, before eating and after touching surfaces in public places. Particular attention should be paid to environmental cleaning in healthcare settings, daycares, cruise ships and other institutional settings. The most contagious enteric viruses are the noroviruses because of the low inoculum required to spread disease and stability in the environment. Use of bleach based cleaning is necessary to eliminate noroviruses from surfaces. Hospitalized patients with norovirus should be placed into contact isolation and rooms should be cleaned with chlorine bleach (1000–5000 ppm or a 1:50–1:10 dilution of household bleach).

Hand rubbing with alcohol based hand sanitizers may reduce contact with some enteric viruses but is ineffective for Noroviruses. Handwashing with soap and water for 20 s is recommended.

Because of the high infant morbidity associated with rotaviruses, a vaccine has been developed. Rotavirus vaccine should be administered to all infants without a contraindication. A live quadrivalent Rotavirus vaccine (Rotashield-Wyeth) was initially licensed in the United States in 1998. Though effective, postmarketing surveillance indicated an increased incidence of intussusception 3–20 days after vaccine administration. This vaccine was removed from the market in 1999 and replaced in 2006 with RotaTeq (RV5 Merck) and Rotarix (RV1GSK), live oral reassortment (RotaTeq 5 viruses; Rotarix, 1 strain) vaccines. The RotaTeq vaccine is given in three doses at 2, 4 and 6 months of age and achieves a 98% reduction in severe RGE, 74% against any severity GE in the first year and a 96% reduction in hospitalizations. Rotarix is a two dose vaccine given as oral drops at 2, 4 months. It has 85%–96% protection against severe disease and a 96% reduction in hospitalizations through two seasons (vaccines, n.d.; Burnett et al., n.d.; Tate and Parashar, 2014).

Adenoviruses also are often resistant to common disinfectants and may remain infectious for prolonged periods on medical instruments and surfaces.
Prognosis

In general viral GE is a self-limited infection and complete recovery is expected if hydration can be maintained.

See Also: Diarrhea; Anti-Diarrheal Drugs

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