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388

ROTAVIRUSES, NOROVIRUSES, AND OTHER GASTROINTESTINAL VIRUSES

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DEFINITION

Viruses are the agents of acute infectious gastroenteritis, a syndrome of vomiting, watery diarrhea, or both that begins abruptly in otherwise healthy persons. Two distinct viruses account for the majority of cases. Rotaviruses are the principal agent of sporadic, severe gastroenteritis in young children and are responsible for the death of approximately 1600 children daily worldwide, mainly in developing countries (Fig. 388-1). Noroviruses are the principal agent of epidemic infectious gastroenteritis in both infants and adults. For example, outbreaks of gastroenteritis in closed settings, such as cruise ships and nursing homes, are a typical manifestation of norovirus infections. However, noroviruses are also a common cause of sporadic, severe gastroenteritis in young children.

The Pathogens

Noroviruses

Noroviruses, which are one of the five genera of the Caliciviridae family, are nonenveloped, icosahedral viruses with a relatively small, positive-sense, single-stranded RNA genome. The norovirus genus is further classified into five genogroups (GI to GV), only three of which (GI, GII, and GIV) are known to infect humans. GIII and GV viruses infect bovines and mice, respectively, and to date these animal viruses have not been shown to infect humans. Viruses in each genogroup are further divided into genotypes (more

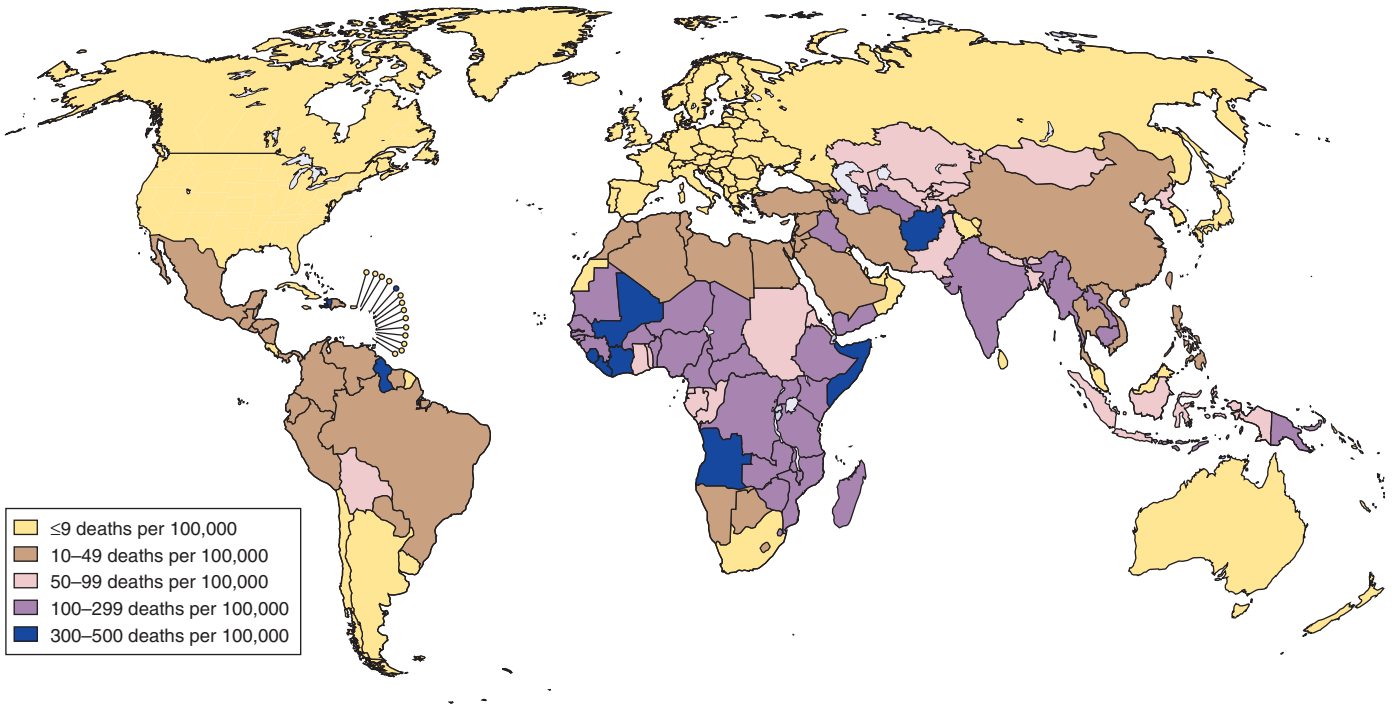

FIGURE 388-1. Mortality rate associated with rotavirus disease worldwide. (Based on World Health Organization data and modified with permission from Danchin MH, Bines JE. Defeating rotavirus? The global recommendation for rotavirus vaccination. *N Engl J Med.* 2009;361:1919-1921.)

TABLE 388-1 EPIDEMIOLOGIC AND CLINICAL FEATURES OF NOROVIRUS AND ROTAVIRUS

	NOROVIRUS	ROTAVIRUS	ASTROVIRUS
Epidemics	Occurs year-round; outbreaks tend to peak in cold weather	Year-round in equatorial countries; winter peak in others	Winter epidemics in children and endemic year-round
Key driver of epidemics	Antigenic drift strains promoted by population-based immunologic pressure	Size of the susceptible birth cohort	Unknown
Transmission	Fecal-oral, water, and food-borne outbreaks	Fecal-oral	Fecal-oral
Severity of diarrhea in children	Generally mild but can be severe	Most severe	Milder than rotavirus or noroviruses
Reservoir	Humans are the only known reservoir of noroviruses that infect humans	Mostly humans, but rotaviruses from farm animals and pets (especially in developing countries) infect humans	Humans are the only known reservoir of astroviruses that infect humans
Prevention	Viral protein 1-based vaccine in development	Several vaccines available	No vaccine in development
Age predisposition	All ages	Children <5 years; disease transmission in older family contacts is low (<25%)	Generally children, but adults may also get disease

VLP = Norwalk virus (NV) virus-like particles.

than 25 have been described) and subgroups. Norwalk virus is a prototype genogroup I genotype 1 (GI.1) virus. The norovirus genome is approximately 7.7 kilobases in size and consists of three open reading frames, the first of which encodes the nonstructural proteins that are essential for virus replication. The second open reading frame encodes the major capsid protein, viral protein 1 (VP1). When it is expressed as a recombinant protein, 180 molecules of VP1 autoassemble into virus-like particles that are critical to the study of noroviral epidemiology and immunity. Human noroviruses have not yet been adapted to cell culture, so diagnosis generally depends on amplification of virus genes by the polymerase chain reaction (PCR; see later).

Rotavirus

Rotaviruses, which belong to the family Reoviridae, are large, icosahedral, nonenveloped viruses with a segmented, double-stranded RNA genome and a triple-layered protein coat. Rotaviruses are classified into groups A through G on the basis of the presence of cross-reactive antigenic epitopes and their overall genetic relatedness. Group A rotaviruses are the principal enteric pathogen of humans and many other species. Group B viruses have been identified sporadically in outbreaks of adult diarrheal illness in China and more recently in studies of children with sporadic gastroenteritis, principally in India. Group C rotaviruses are relatively infrequently associated with diarrheal disease in humans and animals around the world. Groups D through G rotaviruses have been isolated only from animals, primarily avian species. Rotaviruses are 100-nm particles that have three concentric layers of proteins: the core is composed of VP1, VP2, and VP3 and the segmented, double-stranded RNA genome; the intermediate layer is formed by VP6, the most abundant and antigenic structural viral protein; and the external layer is composed of VP7 and VP4. The genome is composed of 11 segments of double-stranded RNA that together are approximately 18 kilobases and encode six structural and six nonstructural proteins. As is the case among virtually all other RNA viruses, the rotavirus RNA polymerase is error prone and, along with selective pressure such as the evolution of immunity, drives viral diversity. For rotaviruses, gene reassortment, which is the mixing of gene segments from different parental viruses in cells coinfected by two or more strains, and rearrangement of the viral genome also contribute to genetic diversity. Reassortment of gene segments between animal and human rotavirus strains also occurs in natural settings, especially in less developed countries.

Other Agents

Other viral agents that cause human acute infectious gastroenteritis that is difficult to distinguish from disease caused by rotaviruses and noroviruses include the sapovirus (like norovirus, a member of the Caliciviridae family), enteric adenoviruses (Chapter 373) belonging to types 40 and 41, and astroviruses (Table 388-1). The frequency of detection (by PCR assays) of these viruses in individuals with acute gastroenteritis depends on the setting, but

they are almost always detected less frequently than rotaviruses and noroviruses. Coronaviruses (Chapter 374), toroviruses, picobirnaviruses, picornavirus (Chapter 387), bocavirus, parechoviruses, and pestiviruses have also been isolated occasionally from persons with acute gastroenteritis, but their roles as causative agents of enteric disease remain uncertain. Among patients with acute gastroenteritis, no etiologic agent is found in approximately 25 to 50% of cases.

EPIDEMIOLOGY

Norovirus

Over time, noroviruses appear to undergo antigenic drift in response to the acquisition of immunity in the general population, much like influenza viruses. At present, gastroenteritis cases around the world are most frequently caused by the GII.4 norovirus strain, but new strains generally evolve every 2 to 4 years owing to antigenic drift. Outbreaks frequently take place in settings of close human contact, such as military establishments, cruise ships, nursing homes, and schools, especially in cold and dry weather (see Table 388-1). Viral spread is enhanced by the very high level of infectivity of noroviruses, as data suggest that 1 to 10 particles constitute an infectious dose.

Noroviruses also are responsible for about 12% of sporadic gastroenteritis in children younger than 5 years in both developed and developing countries. Overall, it is estimated that noroviruses annually cause 900,000 outpatient visits and 64,000 hospitalizations among children in developed countries as well as up to 200,000 deaths of children younger than 5 years in developing countries.

Rotavirus

The incidence of rotaviral disease is similar in children in both developed and developing countries, suggesting that measures such as access to clean water will not replace the need for an effective vaccine. Before the introduction of an effective vaccine, rotavirus was estimated to be responsible for about 600,000 annual deaths worldwide. In developed countries, rotavirus rarely is fatal; but before the introduction of vaccines in the United States, it resulted in hospitalization for rotavirus-mediated gastroenteritis in about 1 in 75 children by 5 years of age.

In the temperate zones of the world, rotaviral infection occurs primarily during epidemic peaks in the cooler months of the year (see Table 388-1). This pattern is not seen, however, in countries within 10 degrees of the equator, where infection occurs in an endemic fashion year-round. Before the introduction of rotavirus vaccination, a yearly wave of rotaviral illness spread across the United States and Europe following peculiar spatiotemporal patterns. In the United States, this pattern of spread has been correlated with variation in birth rates, thereby suggesting that the number of babies experiencing their first infection is one of the primary drivers of rotavirus epidemics. The high birth rates in developing countries may also influence the differential epidemiologic distribution of rotaviruses. Antibodies against the outer capsid proteins are the basis of serotypic classification of rotaviruses into G (glycoprotein, VP7) and P (protease-sensitive, VP4) serotypes. For technical reasons, P serotyping reagents are infrequently available, and classification is based on the P genotype (provided in brackets). Worldwide, most human infections are caused by five types of group A rotavirus; P[8]G1 is by far the most common (approximately 53% of strains), followed by P[8]G3, P[4]G2, P[8]G9, and P[8]G4. In some developing areas like India, Brazil, and Africa, P[6]G9, G5, and G8 rotaviruses, respectively, are most frequently encountered. Some human rotavirus strains may have arisen after reassortment with bovine or porcine rotaviruses. A high prevalence of G12 viruses has recently been observed in several countries, thereby suggesting that this serotype may be an emerging rotavirus strain.

PATHOBIOLOGY

Norovirus

Histo-blood group antigens (HBGAs) are the receptors for noroviruses and determine susceptibility to disease in a strain-specific manner. The HBGAs are complex carbohydrate oligosaccharides linked to proteins or lipids that are expressed on the mucosal epithelia of the digestive tract. All three major families of HBGA, the ABO, Lewis, and secretor families, are involved in binding noroviruses. The secretor status of a person is controlled by the fucosyltransferase 2 (*FUT2*) gene. Secretor-negative individuals are specifically resistant to infection with the Norwalk virus (GI.1) and some GII viruses.

Although norovirus RNA has been detected in the blood stream of up to 15% of patients with norovirus gastroenteritis, the site of primary viral replication is most probably in the gastrointestinal tract. Consistent with the strong association of vomiting with norovirus disease, gastric emptying is delayed. Proximal jejunal biopsy specimens show blunting of the villi with crypt cell hyperplasia and cytoplasmic vacuolation, sometimes with an increase in epithelial cell apoptosis. A functional alteration of the epithelial barrier is likely to occur. Unknown at present is the effectiveness and persistence of immunity in the context of natural infection, in which the infectious dose is generally quite low.

Rotavirus

Rotaviruses replicate in the villus tip cells of the small bowel, where the pathologic process includes shortening and atrophy of the villi, mononuclear infiltration in the lamina propria, and distention of the cisternae of the endoplasmic reticulum. However, the severity of clinical disease is not directly related to the extent of intestinal disease; rather, it is related to levels of viral RNA in stool.

During the initial phases of the disease, altered intestinal secretion, motility, and permeability contribute to the pathophysiologic mechanism of diarrhea. Later in the course of disease, malabsorption can occur. Rotaviral NSP4 is a viral enterotoxin that mediates, at least in part, the early secretory components of the diarrhea. It has also been postulated that viral infection increases intestinal motility by stimulating the enteric nervous system, possibly through NSP4. Whether and to what degree the enterotoxic effect of NSP4 is clinically relevant in children or other animal species remains to be determined. Infected individuals have a short period of viremia, but its clinical consequences are unclear other than correlating with the level of fever.

Rotavirus serum IgA levels measured shortly after natural infection in children generally correlate with intestinal IgA levels and appear to correlate with protection. One explanation for recurrent rotavirus (and norovirus) infections is that protection from reinfection is mediated by intestinal IgA, which is not long-lasting in humans. Another explanation is that protection is dependent on neutralizing antibodies to one or both of the highly variable outer rotaviral proteins. However, a monovalent P[8]G1 vaccine induces significant protection against strains with different serotypes, thereby supporting the conclusion that protective immunity to rotavirus infection is, in part, heterotypic.

CLINICAL MANIFESTATIONS

Norovirus

The clinical manifestations of norovirus infection are variable and depend in part on the age of the individual infected. About one third of infections are asymptomatic, but symptoms include diarrhea, nausea, vomiting, abdominal cramps, fever, and malaise that generally persist for 2 to 3 days. In children younger than 11 years, disease typically begins with the sudden onset of vomiting and can last 4 to 6 days. Virus can be shed in low titers for up to 8 weeks from otherwise healthy individuals and for more than a year in patients with severe immunodeficiency syndromes. In neonates and premature infants, vomiting often is not a symptom, and infection has been associated with necrotizing enterocolitis. To support the diagnosis of norovirus outbreaks, the following four criteria have been proposed: (1) vomiting in more than half of affected persons; (2) mean (or median) incubation period of 24 to 48 hours; (3) mean (or median) duration of illness of 12 to 60 hours; and (4) absence of bacterial pathogens in stool culture.

Rotavirus

Rotavirus diarrhea and dehydration tend to be more severe than illness caused by the other childhood enteric pathogens. Rotavirus diarrhea is watery, persists for approximately 5 days, is often preceded by the sudden onset of vomiting, and is frequently accompanied by fever and dehydration. The incubation period of rotavirus is estimated to be less than 48 hours. Viral excretion in feces persists for 10 days in the majority of children and rarely can persist for up to 57 days. Excretion times are longer on examination by sensitive PCR-based assays rather than solid-phase immunoassay. By the age of 5 years, virtually all children have acquired immunity to rotavirus, and severe disease after this age is uncommon.

DIAGNOSIS

Norovirus

Reverse transcription–PCR (RT-PCR) is currently the procedure of choice to detect norovirus in clinical specimens, in food, and in water. Although enzyme-linked immunosorbent assays (ELISAs) to detect noroviruses are available in Europe, their sensitivity is genotype dependent, and diagnostic

specificity and sensitivity vary on the basis of the diversity of the circulating strains in the population. Moreover, these immunoassays are not easily adaptable for detection of new strains. Norovirus RNA is detected by RT-PCR in stool samples of up to 16% of healthy individuals, a finding that complicates the diagnosis of norovirus gastroenteritis. Although the relationship between disease symptoms and viral load has not been fully established, a quantitative real-time RT-PCR has been proposed to establish a relative threshold of positivity for attributing disease to norovirus.

Rotavirus

Before the introduction of the rotavirus vaccine in developed countries, well above 50% of the moderate to severe diarrheal episodes in young children during the rotavirus "season" were due to rotavirus. In tropical countries, the presence of other enteric pathogens and the absence of seasonal occurrence of rotaviral disease make it more difficult to determine which diarrheal episodes are caused by rotavirus without a diagnostic assay. Numerous ELISAs for rotavirus are commercially available, and these are generally sensitive, specific, and easy to use under most conditions. PCR has increased sensitivity for detection of rotavirus and has permitted easy typing of viruses. With PCR-based methods, however, up to 29% of healthy children younger than 1 year may be rotavirus positive, so it is difficult to associate the detection of the virus with gastroenteritis. Thus, ELISA or quantitative RT-PCR (using a threshold level as for norovirus) is preferable for diagnosis of rotavirus gastroenteritis.

PREVENTION

Norovirus

The development of a norovirus vaccine for humans is a challenge owing to the great degree of antigenic heterogeneity among circulating strains, the propensity of noroviruses to undergo antigenic drift, and the lack of known correlates of protection. High percentage alcohol-based sanitizers (99.5% ethanol) and 10% povidone-iodine antiseptics are superior to other alcohol-based sanitizers at reducing norovirus contamination. Simple household antimicrobial hand soap and handwashing with tap water also decrease viral contamination.

Rotavirus

Rotavirus vaccines have been based on two different approaches. One type of vaccine uses a mixture of reassortant viruses, each part human rotavirus and part animal rotavirus, to provide attenuation.[1,2] Another approach uses a single attenuated human virus.[3,4] Neither type of vaccine prevents subsequent rotavirus infection or mild illness, but both types prevent severe illness.

The first vaccine (Rotashield, Wyeth-Lederle), which used a mixed rhesus-human rotavirus, was effective and licensed for use in the United States, but it was subsequently withdrawn from the market because of its association with intussusception. Subsequently, two second-generation vaccines were shown in large studies to be safe without detectable risk of intussusception, effective, and cost-effective in developed and developing countries. RotaTeq (Merck) is a modified pentavalent vaccine made of bovine and human virus. Rotarix (GlaxoSmithKline) is a monovalent attenuated human virus vaccine.

Protection rates in developed and middle-income countries for each vaccine are similar, varying from 70 to 80% against any rotavirus disease to 90 to 100% against severe gastroenteritis.[5,6] These two vaccines may be only about 50% efficacious against severe diseases in the poorest developing countries.[5] However, even with the reduced effectiveness, the two licensed vaccines are still cost-effective. The World Health Organization now recommends the routine use of these vaccines.

TREATMENT

Rx

Because both norovirus and rotavirus disease resolves within days without treatment, the basic therapeutic goal is to prevent acute dehydration. The recommended oral rehydration salts solution, which now has an osmolarity of 331 mmol/L, is as effective as higher osmolarity solutions.[6] After rehydration, rapid age-appropriate refeeding is recommended. Rotavirus disease induces self-limited intestinal lactase deficiency, but lactose-containing products, particularly maternal milk, should not be withheld.

Passive oral immunotherapy with diverse preparations of immunoglobulins can shorten the duration of rotavirus infection but probably is economically feasible only for immunodeficient patients or low-birthweight infants. *Lactobacillus*, a bacterium present in yogurt, is safe and, in limited studies, appears moderately effective for treatment of acute rotavirus gastroenteritis. Nonetheless, different preparations of lactobacilli vary greatly in dose of bacteria, and a general recommendation on their use has not been issued. Several studies in developing countries have shown that zinc supplementation (10 mg/day for infants younger than 6 months and 20 mg/day for older children) is useful for the treatment and prevention of diarrhea, but further studies are needed to determine whether treatment will be useful in all developing and developed countries.

At present, no pharmacologic treatment of rotavirus or norovirus diarrhea is recommended. Racecadotril (4.5 mg/kg per day), an enkephalinase inhibitor that acts on the enteric nervous system, has been shown to be useful as an adjunct to treat rotaviral diarrhea in several small studies. Ondansetron (0.15 mg/kg per day), a serotonin antagonist, is effective in reducing the emesis from gastroenteritis during the phase of oral rehydration. In several small studies, nitazoxanide (15 mg/kg per day) was helpful in the treatment of rotavirus gastroenteritis. More studies are needed before any of these various preparations can be generally recommended for treatment of rotavirus diarrhea.

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SUGGESTED READINGS

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