Norwalk Virus and Other Caliciviruses

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General Concepts

Clinical Manifestations

Norwalk virus and other caliciviruses produce infections that cause acute diarrhea and vomiting (gastroenteritis), abdominal cramps, myalgias, malaise, headache, nausea, and low-grade fever.

Structure

Norwalk virus is a round, nonenveloped, 27-nm virion that belongs to the Caliciviridae family. To date it is not cultivatable in vitro. Its nucleic acid contains single-stranded, positive-sense RNA. It has a single structural protein characteristic of a calicivirus. Other human calicivirus virions are similar but some are slightly larger and have surface cup-shaped indentations.

Classification and Antigenic Types

The caliciviruses are grouped on the basis of morphology, size, protein profile, and nucleic acid. Norwalk virus and some other human caliciviruses share considerable genetic homology but are antigenically distinct.

Multiplication

The single, positive strand of Norwalk virus RNA contains three open reading frames, one of which is known to encode the single capsid protein.

Pathogenesis

Infection is by oral ingestion. Viruses grow in the small intestine, causing transient lesions of intestinal mucosa, and are shed in feces.

Host Defenses
Serum and local gastrointestinal tract antibodies against Norwalk virus are not protective, but represent risk factors or markers for illness.

**Epidemiology**

About half of the outbreaks of acute infectious nonbacterial gastroenteritis in the United States are due to Norwalk virus. The disease occurs worldwide and is common in older children and adults. Outbreaks occur in camps, schools, nursing homes, etc., and are associated with contaminated foods and water and uncooked foods.

**Diagnosis**

The diagnosis is suggested by acute gastroenteritis in a community outbreak setting. It may be confirmed by antigen detection or observation of an antibody rise; these techniques are available only in research laboratories.

**Control**

No antiviral therapy or vaccine is available.

**INTRODUCTION**

The caliciviruses are small, nonenveloped RNA viruses that have characteristic cup-shaped depressions on a spherical capsid surface; hence their name, which is derived from calyx or chalice. Caliciviruses have a distinctive structure, sometimes described as a star of David, and are also distinctive in their size (27 to 35 nm), in having only a single major polypeptide, and in the functions of the single-stranded RNA genome. They produce mucocutaneous and respiratory tract lesions in several animal species, including swine, pinnipeds, and cats, and they have been grown in cell culture, purified, and characterized.

Human caliciviruses have not been cultivated in vitro. However, the genome of some human strains has been cloned and sequenced. Human caliciviruses are often observed in patients with diarrheal illness. The best known of the human agents is Norwalk virus, which is a major cause of epidemics of self-limited diarrhea and vomiting in school children and adults. Resistance to the infection is unrelated to serum or local gut antibody.

**Clinical Manifestations**

Norwalk virus produces a classic clinical picture of acute diarrhea and/or vomiting (gastroenteritis) in older children and adults. This common illness has an abrupt onset and is accompanied by a varying combination of signs and symptoms, including abdominal cramps, myalgias, malaise, headache, nausea, and low-grade fever. The
disease usually resolves spontaneously within 24 to 48 hours. Fatalities are very rare and are confined to elderly or debilitated individuals. Some other human caliciviruses produce a clinical syndrome similar to that of Norwalk virus, but, similar to rotavirus gastroenteritis, some virus strains also cause diarrhea and vomiting in infants and young children.

**Structure**

Norwalk virus is a small (diameter, 27 nm), round, nonenveloped virus with an amorphous surface structure possessing a feathery, ragged outline. The virion contains single-stranded, positive sense RNA of the size of about 7.5 kb. Norwalk virus is recognized in human stool specimens by immune electron microscopic or immunoassay techniques.

The virus, purified from feces, contains a single structural protein with a molecular weight of about 60,000, characteristic of the single-stranded, RNA-containing calicivirus group.

Some other human calicivirus strains are described as being round and slightly larger than Norwalk virus in feces (31 to 35 nm in diameter). They have cup-shaped indentations on the virion surface, which make the virus indistinguishable from well-characterized caliciviruses of animals, and also contain a single structural protein of a similar molecular weight to that of Norwalk virus.

**Classification and Antigenic Types**

On the basis of their morphology, size, protein profile, and nucleic acid, Norwalk virus and other human caliciviruses are classified in the family Caliciviridae. Several viruses are described that share virologic characteristics with Norwalk virus as well as association with epidemics or family outbreaks of acute gastroenteritis. Like Norwalk virus, these viruses are named after the location of the outbreak from which they are derived (Norwalk, Ohio; Hawaii; Snow Mountain, Colorado; Taunton and Southampton, England; Otofuke and Sapporo, Japan). These viruses share considerable genetic homology with Norwalk virus. However, several of these other human caliciviruses are antigenically distinct on the basis of immune electron microscopy studies. Despite this distinctiveness, some patients recovering from gastroenteritis due to other caliciviruses mount antibody responses to Norwalk virus, suggesting that these viruses share some immunologic properties.

**Multiplication**

The replication strategy of Norwalk virus is currently being unraveled. Cloning and sequencing of its genome, as well as that of Southampton calicivirus, has revealed a single, positive strand of RNA that contains three open reading frames, one of which encodes the single capsid protein.

**Pathogenesis**

These viruses are ingested orally from contaminated water or foods or are spread from person to person by the fecal-oral route (Fig. 65-1). Norwalk virus was first discovered
in diarrheal stool specimens from patients infected during an epidemic of gastroenteritis that occurred in Norwalk, Ohio, in 1968. The disease was reproduced in adult volunteers, who developed a transient mucosal lesion of the proximal small intestine. Norwalk virus infection seems to spare the large intestine, and thus fecal leukocytes are not present in the stool. Delayed gastric emptying occurs during this infection.

FIGURE 65-1 Pathogenesis of Norwalk virus infection.

**Host Defenses**

Although most adults have serum antibodies to Norwalk virus, the antibodies do not protect them from the disease. In fact, they may be a marker or risk factor for illness. For example, when virus was given to volunteers, one of two types of immune responses occurred. One group of individuals, who lacked appreciable serum or intestinal antibodies, persistently failed to develop illness or to mount antibody responses on initial exposure to the virus and after rechallenge up to 3 years later. A second group of volunteers, who had systemic or local antibodies, developed gastroenteritis on initial exposure and were again susceptible when rechallenged 3 years later. After the illness, these individuals usually developed a short-term immunity that lasted for about 12 weeks. Further studies are needed to ascertain whether genetic susceptibility or the need for repetitive past exposures to the virus plays a role in the pathogenesis of Norwalk virus infection.

**Epidemiology**

Norwalk virus produces nearly 50 percent of all outbreaks of acute infectious, nonbacterial gastroenteritis in the United States. This common syndrome is
characterized by 1 to 2 days of diarrhea or vomiting or both and is the second most common cause of illness in American families, after respiratory tract disease. In developed areas, the illness typically occurs in older children and adults and spares preschool children.

Seroprevalence studies indicate that Norwalk virus infection occurs worldwide. Two-thirds of Americans have serum antibodies, which are uncommon in children and are acquired during early adulthood. The results of antibody studies correlate with the rarity of Norwalk virus infection as a cause of gastroenteritis in infants and young children in the United States. Disease outbreaks among older children and adults occur in camps, schools, nursing homes, military populations, cruise ships, and areas with contaminated drinking or swimming water. The ingestion of raw shellfish or other uncooked foods, such as salads or cake frosting, that have been handled in an unsanitary manner may lead to the disease. Outbreaks of Norwalk virus infection occur throughout the year. Other human caliciviruses appear to share the epidemiological characteristics of Norwalk virus.

Infection is transmitted by the fecal-oral route. Although there is no conclusive evidence that the virus is also spread by the respiratory route, it could be transmitted via aerosolized virus-containing vomitus, in light of the very rapid secondary spread of infection during outbreaks.

**Diagnosis**

The diagnosis is suggested by acute diarrhea and/or vomiting in a community outbreak setting. Norwalk virus may be identified in stool specimens, and antibody can be measured in serum samples by immune electron microscopic or immunoassay techniques. These complex diagnostic methods require the use of limited clinical materials (stools and sera), and can be performed in only a few research laboratories that possess the needed reagents. Viral capsid proteins, recently derived from genetically expressed cloned Norwalk virus genome, are immunogenic and may prove useful in assays to detect human antibodies. Norwalk virus RNA has recently been detected in stool samples, and PCR techniques to perfect these assays are being developed.

**Control**

No specific antiviral therapy is available for Norwalk or other human calicivirus gastroenteritis. Prospects for vaccine development seem poor because of the complex pattern of clinical immunity to Norwalk virus. The development of a vaccine that produces long-lasting immunity seems unlikely because such immunity has been found to be absent in rechallenged volunteers. Hand washing and careful monitoring of water purification are the most important measures in the control of infection.

**REFERENCES**


