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Viral Gastroenteritis

John E. Herrmann, Ph.D.
Division of Infectious Diseases
University of Massachusetts Medical School
Worcester, MA 01605

Viral gastroenteritis, a disease of major public health importance in people of all ages in both developed and developing countries, occurs in both epidemic and endemic forms. Viruses that have been associated frequently with gastroenteritis include rotaviruses, Norwalk and Norwalk-like viruses, enteric adenoviruses, caliciviruses, astroviruses, enteric coronaviruses, and unclassified small round viruses of 27 to 32 mm in diameter (Table 1). The viruses that have been shown to be most often involved in gastroenteritis to date are rotaviruses and viruses in the Norwalk virus group. The rotaviruses are the major viral cause of gastroenteritis in infants and young children and are an important viral cause of infant mortality in many areas of the world. Viruses in the Norwalk group have been associated most often with epidemics of gastroenteritis among adults and older children.

None of these viruses was known prior to 1972, most likely because these agents cannot be cultivated by standard cell-culture techniques. With specialized techniques, isolation and propagation of rotaviruses (1), enteric adenoviruses (2), and astroviruses (3, 4) are now readily accomplished, and cultivation of calicivirus and enteric coronavirus has been reported (5, 6). All of the gastroenteritis viruses were first recognized by electron microscopy (EM), and positive identification of the viruses that cannot be cultivated has been based, ultimately, on EM or immune EM (IEM).

Epidemiology and Clinical Aspects

Rotaviruses

Rotaviruses are a major cause of gastroenteritis in infants worldwide and, in temperate climates, may be responsible for nearly half of infant hospitalizations during the winter months. There are four established serotypes of human rotaviruses, but all share a common group antigen. In recent years, viruses that have rotavirus morphology but do not have the group antigen have been discovered and have been referred to as pararotaviruses, novel rotaviruses, or non-group-A rotaviruses (conventional rotaviruses are now classified as group-A rotaviruses). The vast majority of rotavirus gastroenteritis, however, appears to be caused by the conventional types. Transmission of the viruses is thought to be primarily by the fecal-oral route, although transmission through food and water has been suggested. Both virus-specific IgA and virus antigen have been detected in pharyngeal secretions (7), which suggests that transmission may occur via a respiratory route as well. The maximal viral shedding in stools occurs from 2 to 5 days after the onset of diarrhea (7).

The major clinical symptoms usually include vomiting, diarrhea, mild dehydration, and in about three-fourths of cases, fever of 37.9°C to 39°C or higher may be seen. The duration of the disease is generally 3 to 9 days, and the mean time of hospitalization, when severe enough to be required, is 4 days. Nosocomial infections may be responsible for approximately 20% of rotavirus infections in hospitals (8). Rotavirus infections in adults are usually mild, but severe symptoms have been reported in both elderly patients and apparently normal young adults. Infections due to non-group-A rotaviruses have caused severe symptoms in adults in China (9).

In developing countries, infant mortality due to rotavirus diarrhea is thought to be high; mortality due to rotavirus infection in developed countries has been reported, but is rare (10). Rotavirus infection may also be

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TABLE 1. Major human gatroenteritis viruses

Virus	Year described	Virion diameter (nm)	Nucleic acid type[a]
Norwalk virus	1972	27–32	unknown
Rotavirus	1973	70–75	dsRNA
Enteric coronavirus	1975	100–150	ssRNA(+)
Calicivirus	1976	27–32	ssRNA(+)
Astrovirus	1978	27–32	ssRNA(+)
"Small round viruses"	1978	27–32	unknown
Otofuke/Sapporo agents	1979/81	35–40	unknown
Enteric adenovirus	1979	70–80	dsDNA

[a] ds = double-stranded; ss = single-stranded.

asymptomatic in approximately half of children under 2 years old. Although asymptomatic rotaviral infection is a frequent occurrence in neonates and the recovery of virus from stools of patients with diarrhea may not be significant, rotavirus infection is usually significantly associated with symptomatic disease in children over 6 months old.

Norwalk Virus

Norwalk virus and Norwalk-like viruses have been implicated in epidemics of gastroenteritis occurring in families, communities, schools, camps, institutions, and cruise ships. The outbreaks are often common-source, involving contaminated raw shellfish or other food, and affect older children and adults as well as infants and young children. The viruses in this group include, in addition to Norwalk virus, Snow Mountain virus, Hawaii virus, MC virus, and Taunton virus. All of these viruses cause similar clinical symptoms, including nausea, vomiting, and diarrhea in approximately 70% of patients. Epidemics occur year round but are most frequent in the winter and early spring. For this reason, Norwalk virus outbreaks were once referred to as "winter vomiting disease." The course of the disease is usually 1 to 3 days but may last more than 3 days in some people. Hospitalization is rarely required, except for patients with severe dehydration or other debilitating diseases. In approximately 30% of patients, symptoms may include headache, fever, and abdominal pains or cramps. Norwalk virus infection may also be asymptomatic. Peak virus content in stools occurs during the onset of illness and is below detectable levels 3 days later (11). The incubation period in both natural infections and volunteer studies is 18 to 48 hours, and symptoms usually last for 24 to 28 hours.

Enteric adenoviruses

Two adenovirus serotypes (40 and 41) have been commonly identified in the stools of infants and young children with gastroenteritis in both temperate (12) and tropical (13) countries. The percentage of gastroenteritis cases due to enteric adenoviruses has ranged in various reports from 1.5% to 13.5%. The major symptom is diarrhea, which may last up to 9 days. Fever and vomiting are usually mild. Respiratory symptoms have also been reported. Other types of adenoviruses have occasionally been isolated from stools, but only types 40 and 41 are consistently associated with gastroenteritis. These enteric virus types also appear in higher concentrations in stools than other adenovirus types, and, like rotaviruses, may exceed 10^{11} particles/g feces. As with rotaviruses, transmission of these viruses appears to be person-to-person, and no water- or food-borne outbreaks have been reported to date.

Other viruses

Some of the other gastroenteritis viruses (astroviruses, caliciviruses, coronaviruses, and small round viruses) have been implicated in clinical illness, but their frequency and medical importance are less well characterized than those of the rotaviruses, Norwalk viruses, or enteric adenoviruses. In an EM study of stools from children in Buffalo, New York, involving 304 cases of viral gastroenteritis (of 1,160 total cases of gastroenteritis), rotavirus was found in 230 (76%), adenovirus in 29 (10%), astrovirus and small round viruses in 20 (7%), and calicivirus in 5 (2%) (14). Other gastroenteritis viruses, also detected by EM, include the "Sapporo agent" and the antigenically related "Otofuke agent," both identified in Japan, and miscellaneous "small-round viruses" of 20 to 32 nm in diameter.

Coronaviruses have been associated primarily with respiratory illness but also have been implicated in enteric disease, especially in neonates. Resta et al (6) have isolated coronaviruses from stools of infants with necrotizing enterocolitis. However, a number of investigators have reported finding coronavirus-like particles in stools as frequently in healthy subjects as in those with clinical symptoms of gastroenteritis. Further studies are required to clarify the role of coronaviruses in gastroenteritis.

The clinical symptoms of astrovirus infection are similar to those caused by rotaviruses, and epidemics have occurred primarily in younger age groups, although outbreaks have been reported in convalescent homes. The Marin County virus, previously included in the Norwalk virus group, has now been shown to be an astrovirus (15).

Calicivirus infections are similar to those of rotavirus, both in clinical

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symptoms produced and in their epidemiology in younger age groups. Calicivirus has also been involved in shellfish-borne outbreaks of gastroenteritis among adults, and one outbreak of illness has been detected among residents of a home for the elderly. Duration of calicivirus illness is usually 3 to 5 days. Human calicivirus has been shown by serological studies to be related to Norwalk virus by use of a blocking radioimmunoassay (RIA) technique (16).

Diagnosis

Until immunoassays for rotavirus antigen detection were developed, EM or IEM were the major techniques used. These methods remain important for detecting gastroenteritis viruses and for standardizing new detection techniques as they are developed. Serologic techniques, based primarily on seroconversion rather than IgM detection, have also been used and are important for identifying outbreaks of gastroenteritis due to the Norwalk group of viruses. Human rotaviruses and astroviruses can also be identified by their isolation from stool samples in cell cultures with the aid of proteolytic enzymes, and enteric adenoviruses can be isolated in cell cultures such as Graham 293 cells.

Rotavirus

Among the tests that have been developed for diagnosing rotavirus infection, antigen detection by enzyme-linked immunosorbent assay (ELISA) is now the preferred method, because it has been extensively evaluated, found equivalent in sensitivity to EM, and is simple to perform. Numerous commercial ELISA test kits are available for diagnosing group-A rotavirus infections. Latex agglutination tests for detecting rotavirus antigen directly in stool samples also have been developed and are available from several commercial sources. The agglutination tests can usually be done more rapidly than ELISA tests, are convenient to use, but may be far less sensitive than the ELISA assays. A recent evaluation of nine widely available commercial immunoassays (5 ELISAs and 4 agglutination tests) for rotavirus diagnosis demonstrated that the ELISA tests that use monoclonal antibodies are clearly the most sensitive and specific (17). Assays based on nucleic acid probes are also commercially available (Molecular Biosystems, Inc.) but do not appear to offer any advantage over monoclonal antibody ELISA tests for routine clinical diagnosis.

Enteric Adenoviruses

ELISA tests using both polyclonal sera and monoclonal antibody specific for detection of each of the enteric types (40 and 41) in stools have been described (18, 19). A commercially available ELISA that uses monoclonal antibodies to the enteric types has recently become available (Cambridge BioScience Corporation). Direct detection of adenovirus DNA in stools by gel electrophoresis also has been reported, but we have found this method to be of low sensitivity. The procedure is, however, the method of choice for definitive identification of adenovirus types after isolation in cell cultures.

Other Viruses

ELISA tests have been developed both for Norwalk virus antigen and a member of the Norwalk virus group, Snow Mountain virus (20, 21). All of the tests use human immune serum as the source of virus-specific antibody and virus-positive stool as a control. Unfortunately, these requirements restrict use of these tests to the few laboratories possessing the reagents. Monoclonal antibodies reactive with astroviruses by ELISA have been prepared (4), but their efficacy in detecting virus in stools has not yet been established. A polyclonal ELISA reagent has been described for calicivirus antigen detection (22), but its utility in clinical diagnosis requires further evaluation.

Therapy and Prevention

Specific antiviral therapy for viral gastroenteritis is not presently available. Therapy, therefore, is directed at preventing severe dehydration and electrolyte imbalance. Intravenous fluid administration is well established as an effective therapy, but in recent years, an oral rehydration salt(s) solution has been shown to be equally effective, at least for rotavirus gastroenteritis. Oral rehydration of patients can be achieved using glucose or sucrose solutions containing electrolytes, such as the standard World Health Organization WHO formula. Ready-to-use oral electrolyte solutions are also commercially available.

The importance of gastroenteritis as a cause of infant morbidity and mortality in many areas of the world is well recognized, and because rotaviruses have been shown to be important in this disease syndrome for some time, efforts to prevent viral gastroenteritis have been directed primarily toward rotavirus infection. The principal approach taken in recent years has been active immunization with orally administered animal strains of rotavirus. Currently two vaccines have been used most extensively in field trials. One, designated RIT 4237, uses the Nebraska calf diarrhea virus (NCDV) strain of bovine rotavirus, and the other, designated RRV or MMU-18006, uses a rhesus rotavirus strain.

Field trials in Finland with the RIT 4237 vaccine indicated that a high level of protection was afforded and seroconversion occurred in approximately 50% of the vaccine recipients (23). Studies in Butare, Rwanda, with the same vaccine, however, did not show any protective effect, and further, there were no significant differences in the rates of seroconversion among the vaccine and placebo recipients. A similar lack of protection was found in a study of Gambian children. In view of the failure of the RIT 4237 vaccine to provide protection against rotavirus disease in developing countries, clinical studies with this vaccine are no longer being undertaken, and the vaccine is no longer being produced by the manufacturer.

Clinical trials with the rhesus rotavirus vaccine have not been as extensive as those with the NCDV vaccine, and the rhesus vaccine has not been directly compared with the RIT 4237 vaccine for efficacy in preventing rotavirus diarrhea. However, the rhesus rotavirus vaccine has been tested in Finland in a setting comparable with the one used for the bovine rotavirus

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vaccine trials (24). The investigators concluded that the degree of protection was similar to that obtained with the bovine rotavirus vaccine. It has been noted in this study and others that the rhesus rotavirus vaccine may cause side effects similar to natural rotavirus infection and therefore must be given at 100- to 1,000-fold lower infective doses than the bovine vaccine. This has led Vesikari et al (24) to conclude that the bovine strain may be overattenuated and the rhesus rotavirus vaccine too underattenuated for use in humans.

A number of other vaccines have been proposed, including other bovine rotavirus vaccines and vaccines based on reassortant viruses incorporating each of the four human rotavirus serotypes. Whether these would be superior to the RIT 4237 bovine rotavirus vaccine or the rhesus rotavirus vaccine remains to be determined. Clearly, a successful rotavirus vaccine needs to be effective with the population groups at greatest risk for developing severe rotavirus illness, i.e., infants and young children in developing countries. As to the present vaccine situation, sufficient reports are available to conclude that the bovine RIT 4237 and the rhesus rotavirus vaccines are effective in preventing severe rotavirus diarrhea (but not necessarily infection) in developed, temperate zone countries but that no vaccine has as yet been shown to be effective in developing countries.

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Editorial

CAP Workload Recording

Raymond C. Bartlett, M.D.
Director, Division of Microbiology
Department of Pathology
Hartford Hospital
Hartford, CT 06115

The workload recording method devised by the College of American Pathologists (CAP) is the system used in most clinical laboratories (1). With increasing attention being given to cost-effectiveness, administrators have become interested in comparing productivity between laboratories and even between divisions within laboratories. The system is deficient in many ways but has been substantially improved in recent years.

I share the concern expressed by many microbiologists that the "CAP units," which represent the approximate numbers of minutes of work re-