Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
I, 1. Viral causes of gastroenteritis

Umesh D. Parashar and Roger I. Glass

Viral Gastroenteritis Section, Respiratory and Enteric Viruses Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333.

Introduction

Acute gastroenteritis is among the most common illnesses of humans and is caused by a variety of agents, including bacteria, viruses, parasites, toxins, and chemicals. The clinical spectrum ranges from asymptomatic or mild infection to severe, dehydrating illness with a fatal outcome; the latter occurs primarily in young children and in the elderly. In developing nations, children experience more than 3 episodes of gastroenteritis each year, leading to an estimated 2.5-3.2 million deaths [Bern, et al., 1992; Murray and Lopez, 1997]. In industrialized nations, such as the United States, mortality from gastroenteritis is low, but the morbidity and health care costs associated with clinic visits and hospitalizations because of this disease are substantial [Tucker, et al., 1998].

Causative viral agents

Before the early 1970s, no virus had been confirmed as a cause of acute gastroenteritis. The etiologic evaluation of patients with gastroenteritis was limited to investigations for a few bacterial and parasitic agents (e.g., Salmonella, Shigella, Amoeba); consequently, the causes of illness remained unidentified in a majority of cases. Clues that this "diagnostic void" [Flewett, et al., 1987] might be filled by viruses were provided by studies in the 1940s and 1950s that demonstrated the transmission of infection to volunteers challenged with bacteria-free fecal filtrates from persons affected by gastroenteritis [Gordon, et al., 1947]. However, attempts in the 1950s and 1960s to etiologically link a viral agent with gastroenteritis failed.

In 1972, Norwalk virus became the first viral agent identified to cause gastroenteritis. Using immune electron microscopy, Kapikian et. al. identified the 27-nm Norwalk virus particle in stool filtrates of a volunteer challenged with fecal specimens from patients of an outbreak of gastroenteritis [Kapikian, et al., 1972]. In the next few years, electron microscopy (EM) played a key role in the identification or confirmation of many other viruses causing gastroenteritis, such as rotaviruses [Bishop, et al., 1973; Flewett et al., 1973], astroviruses [Madeley and Cosgrove, 1975a, 1975b], enteric adenoviruses
[Wadell, et al., 1987], and human caliciviruses of two different genogroups now called “Norwalk-like viruses” (NLVs) and “Sapporo-like viruses” (SLVs) [Chiba, et al., 2000]. A number of other viruses whose link to human gastroenteritis is not well understood inhabit the gut, including picobirnaviruses [Grohmann, et al., 1993; Rosen, et al., 2000], toroviruses [Koopmans, et al., 1993], coronaviruses, and Aichi virus [Yamashita, et al., 1991; Yamashita, 1999]. The virologic properties of these agents and their EM appearances are presented in Table 1 and Fig. 1, respectively.

Table 1
Virologic properties of and means of detecting viruses associated with gastroenteritis among humans

| Virus               | Family          | Size (nm) | Appearance using electron microscopy (EM) | Nucleic acid | Detection* |
|---------------------|-----------------|-----------|------------------------------------------|--------------|------------|
| Rotavirus           | Reoviridae      | 70        | Wheel shaped, triple-layered capsid       | dsRNA        | EM, EIA, PAGE, RT-PCR, culture |
| Calicivirus         | Caliciviridae   | 28-35     | Small round structured viruses (SRSVs) with calices | ss(+)-RNA   | EM, EIA, RT-PCR |
| Astrovirus          | Astroviridae    | 28-30     | SRSV, star shaped                        | ss(+)-RNA   | EM, EIA, RT-PCR |
| Adenovirus          | Adenoviridae    | 70-80     | Icosahedral capsid                       | dsDNA        | EM, EIA, RT-PCR, culture |
| Picobirnavirus      | Birnaviridae    | 35        | Small round virus                        | dsRNA        | EM, PAGE, RT-PCR |
| Coronavirus          | Coronaviridae   | 60-200    | Pleomorphic with club-shaped projections  | ss(+)-RNA   | EM         |
| Torovirus           | Coronaviridae   | 100-150   | Pleomorphic with torus-shaped core        | ss(+)-RNA   | EM         |
| Aichi virus         | Picornaviridae  | 30        | Small round virus                        | ss(+)-RNA   | Culture, EIA |

* EIA = Enzyme immunoassay, EM = Electron microscopy, PAGE = Polyacrylamide gel electrophoresis, RT-PCR = Reverse transcription-polymerase chain reaction.
Fig. 1. Viral agents of gastroenteritis as seen by electron microscopy. Bar = 100 nm. (Reproduced with permission from Glass et al., 2001)

**Pathophysiology**

The intestinal mucosa consists of arrays of long villi interspersed by crypts near their base. The epithelial cells covering the villi are highly differentiated for purposes of absorption, whereas those in the crypts are less differentiated and act as reservoirs for proliferation and differentiation into absorptive cells. The leading viral agents of gastroenteritis infect the mature enterocytes in the middle or upper villous epithelium of the small intestine. On pathologic examination, shortening and atrophy of the villi, round cell infiltration in the submucosa and lamina propria, and reactive hyperplasia of crypt cells are observed. Vacuolization and shedding of enterocytes from the villous tip may be seen early in infection. The infected epithelium ultimately becomes necrotic and sloughs off. The loss of absorptive villous epithelium coupled with proliferation of secretory crypt cells reverses the inherent absorptive state of the epithelium, resulting in secretory diarrhea with loss of fluids and electrolytes in the lumen. In addition, levels of brush border enzymes characteristic of differentiated cells (e.g., sucrase and lactase) are reduced, leading to accumulation of unmetabolized disaccharides in the gut lumen and consequent osmotic diarrhea [see also Section I, Chapter 2 of this book].

Other pathophysiologic mechanisms have been postulated for gastroenteritis caused by specific viruses. In the early stages of rotavirus infection before significant viral replication in epithelial cells, villous ischemia is induced that produces local changes mediated by endogenous, neuroactive, hormonal substances [Osborne, et al., 1988; Greenberg, et al., 1994]. A non-structural rotavirus protein, NSP4, has been identified as a viral enterotoxin. NSP4 increases the intracellular calcium levels and affects the permeability of plasma membranes, causing an efflux of chloride, sodium, and water, thereby inducing a secretory diarrhea [Ball, et al., 1996; Estes, Section II, Chapter 6]
of this book]. Furthermore, rotavirus appears to evoke intestinal fluid secretion through activation of the enteric nervous system, possibly through triggering by increased intracellular calcium the release of amines or peptides that stimulate dendrites or free nerve endings located beneath the epithelial layer [Lundgren, et al., 2000; Lundgren and Svensson, Section I, Chapter 3 of this book]. In NLV disease, alterations in gastrointestinal motility are believed to play an important role in the pathogenesis of the characteristic nausea and vomiting [Meeroff, et al., 1980].

**Immunology**

The mucosal immune system, quantitatively the largest immune system of the human body, plays a key role in protection against enteric viral infections [Brandtzaeg, 1998 and Section I, Chapter 4 of this book]. This system is characterized by several unique features, including the preferential production, transport, and secretion of IgA at mucosal surfaces. The precursors of mucosal IgA-producing plasma cells originate in organized lymphoepithelial structures (gut associated lymphocytic tissue) located in Peyer’s patches, scattered lymph node follicles, lymphoid cells in the epithelium, and submucosal lymphocytes. Approximately $10^{10}$ immunoglobulin-producing cells are present per meter of bowel, compared with $2.5 \times 10^{10}$ Ig producing cells in bone marrow, spleen, and lymph nodes together. Gut immunocytes produce dimers or polymers of IgA that are linked together by a J-chain. The IgA enters the cytoplasm of intestinal epithelial cells after attaching to receptors on the basolateral surface, acquires a secretory piece, and is secreted into the intestinal lumen.

Protection against rotavirus disease is correlated with presence of virus-specific secretory IgA antibodies in the feces and serum [Coulson, et al., 1990; Coulson, et al., 1992; Matson, et al., 1993; Velazquez, et al., 1996]. Since the presence of virus-specific IgA at the intestinal surface is short-lived, complete protection against natural rotavirus disease is only temporary. The presence of memory B and T cells in the lamina propria is believed to be important in the modification (i.e., reduction in severity) of disease from reinfection [Offit, 1996]. Activation of these memory cells to antibody-producing B cells and virus-specific cytotoxic T cells requires a few days; thus, these effector cells can shorten the duration of illness but cannot prevent it. Studies in mice have shown that both cell-mediated and humoral immune responses have a role in the resolution of rotavirus infection [Franco, et al., 1995; McNeal, et al., 1997; Gonzalez et al., Section II, Chapter 11 of this book].

Studies of the immunity to NLVs have been hampered by the inability to cultivate these viruses in cell lines. Early studies indicated that approximately 50% of persons challenged with NLVs developed illness and as a result acquired short-term homologous immunity against the same strain that was correlated with serum antibody levels [Parrino, et al., 1977]. Some of these studies paradoxically also demonstrated that persons with higher levels of preexisting antibody to NLVs were more likely to develop illness on challenge with virus [Johnson, et al., 1990]. A more recent study using molecular assays confirmed that approximately 50% of volunteers challenged with NLVs are susceptible
to illness, but it also demonstrated that almost 80% become infected, with some of these infections being asymptomatic [Graham, et al., 1994; Gray, et al., 1994].

**Epidemiologic considerations**

**Age**

The etiologic role of viruses is best defined for childhood gastroenteritis (Table 2). Rotaviruses are clearly the leading cause of severe gastroenteritis among children <5 years of age worldwide, causing an estimated 500,000-600,000 deaths each year [Miller, et al., 2000]. With the improvement of detection assays, the role of both NLVs and SLVs in the etiology of childhood diarrhea is being increasingly recognized [Pang, et al., 2000]. Astroviruses and enteric adenoviruses each cause from 2% to 9% of gastroenteritis episodes in children.

Limited data are available regarding the etiologic role of viruses in gastroenteritis among adults. In two recent community-based studies of diarrheal disease among adults in the Netherlands and England [Tompkins, et al., 1999; de Wit, et al., 2001], each of the enteric viruses were detected in 2%-9% of patients (Table 2). Despite the use in these studies of state-of-the-art assays for a variety of enteric pathogens, no organism was identified in 61% and 63% of the patients, respectively. Similarly, in a US study of more than 30,463 patients hospitalized with diarrhea [Slutsker, et al., 1997], a major bacterial pathogen was identified in only 5.6% of cases, and no pathogen could be identified in 91.6% of patients. Ongoing studies may clarify what fraction of these gastroenteritis episodes of unidentified etiology among adults are caused by enteric viruses.

| % children infected | % adults infected |
|---------------------|-------------------|
| **France** [Bon, et al., 1999] | **England** [Tompkins, et al., 1999] | **Finland** [Pang, et al., 2000] | **The Netherlands** [de Wit, et al., 2001] |
| **inpatients / outpatients** | **inpatients** | **community** | **community** |
| (N = 414) (N = 186) | (N = 832) | (N = 761) | (N = 857) |
| Any virus | 72 | NA | 60 | NA |
| Rotavirus | 61 | 56 | 31 | 8 |
| Caliciviruses | 14 | 8 | 30 | 9 |
| Astroviruses | 6 | 9 | 9 | 3 |
| Adenoviruses | 3 | 3 | 6 | 3 |

NA = Not applicable.
Severity of gastroenteritis

In children, the etiologic fraction of gastroenteritis caused by viruses increases with increasing severity of illness. This is well illustrated in a study from Finland [Pang, et al., 2000], in which viruses accounted for only 46% of mild cases of gastroenteritis but as many as 85% of moderate to severe cases. This pattern clearly reflected the above-average severity of rotavirus gastroenteritis, which caused 27% of mild cases, 50% of moderate cases, and 68% of severe cases of gastroenteritis. Based on a clinical scoring system, NLV gastroenteritis was second after rotavirus, whereas disease caused by astroviruses and SLVs was least severe.

Developing versus industrialized nations

Compared with children in industrialized countries, those in developing countries experience 2-5 times as many diarrheal episodes [Glass, et al., 2001]. The difference in the etiologic spectrum of illness in the two settings likely reflects difference in hygiene and sanitation. Thus, bacteria and parasites that are more often spread through contaminated food and water account for a substantial proportion of gastroenteritis episodes in developing countries, whereas enteric viruses that may be spread by airborne droplets or person-to-person contact are ubiquitous and therefore account for a greater proportion of diarrheal episodes in industrialized nations.

Endemic versus epidemic gastroenteritis

Endemic childhood gastroenteritis is caused primarily by rotaviruses and to a lesser extent by SLVs, astroviruses, and enteric adenoviruses. These viruses infect nearly all children in the first few years of life, resulting in long-lasting immunity. The universal nature of infection among children in both industrialized and developing nations suggests that improvements in hygiene and sanitation may not substantially reduce the incidence of disease, and vaccines may offer the best prevention strategy.

Epidemic gastroenteritis is most often caused by the NLVs [Fankhauser, et al., 1998], although outbreaks associated with rotaviruses, astroviruses, and SLVs have been reported. NLV gastroenteritis affects persons of all ages, and volunteers become ill repeatedly on viral challenge. These observations indicate that either immunity to NLVs is short-lasting or the great antigenic diversity of NLVs precludes development of adequate immunity against all strains. Consequently, the development of effective NLV vaccines will be a challenging task, and prevention strategies are currently aimed at interrupting specific modes of transmission, including transmission through contaminated food and water.

HIV-Infected and other immunodeficient persons

Several studies have demonstrated an association between enteric viruses and gastroenteritis in adults infected with HIV while other studies have failed to do so (Table 3).
Table 3
Selected studies of detection of enteric viruses in adults with human immunodeficiency virus infection

| Study                  | No of patients | Viruses       | Method of detection | % detection with/without diarrhea | Association with diarrhea |
|------------------------|----------------|---------------|---------------------|-----------------------------------|--------------------------|
| Cunningham, et al., 1988 | 123            | Rotavirus     | EIA                 | 37/11                             | Yes                      |
|                        |                | Adenovirus    | EM, biopsy, culture | 22/5                              | Yes                      |
| Kaljot, et al., 1989   | 153            | Rotavirus     | EIA                 | 0                                 | No                       |
|                        |                | Adenovirus    | PAGE, EIA           | 5                                 | No                       |
| Grohmann, et al., 1993 | 110            | Overall       | As below            | 35/12                             | Yes                      |
|                        |                | Rotavirus     | EIA                 | 0/0                               | No                       |
|                        |                | Adenovirus    | EIA                 | 9/3                               | Yes                      |
|                        |                | Astrovirus    | EIA/EM/PCR          | 12/2                              | Yes                      |
|                        |                | Calicivirus   | EM                  | 4/1                               | No                       |
|                        |                | Coronavirus   | EM                  | 3/2                               | No                       |
|                        |                | Picobirnavirus | PAGE               | 9/2                               | Yes                      |
| Schmidt, et al., 1996  | 256            | Overall       | As below            | 24/10                             | Yes                      |
|                        |                | Adenovirus    | EM, biopsy          | 9/3                               | Yes                      |
|                        |                | Coronavirus   | EM, biopsy          | 15/7                              | Yes                      |
| Gonzalez, et al., 1998 | 125            | Overall       | As below            | 2/10                              | No                       |
|                        |                | Rotavirus     | EIA                 | 0/0                               | No                       |
|                        |                | Adenovirus    | EIA                 | 2/5                               | No                       |
|                        |                | Astroviruses  | PCR                 | 0/0                               | No                       |
|                        |                | Norwalk virus | EIA                 | 0/0                               | No                       |
|                        |                | Picobirnavirus | PAGE               | 0/4                               | No                       |
| Giordano, et al., 1998 | 88             | Rotavirus     | EIA                 | 0/0                               | No                       |
|                        |                | Picobirnavirus | PAGE               | 9/0                               | Yes                      |
| Giordano, et al., 1999 | 120            | Overall       | As below            | 27/8                              | Yes                      |
|                        |                | Astrovirus    | EIA                 | 4/5                               | No                       |
|                        |                | Adenovirus    | EIA                 | 7/3                               | No                       |
|                        |                | Picobirnavirus | PAGE               | 15/0                              | Yes                      |

In addition, HIV disease can modify the illness caused by the common enteric viruses and also increase susceptibility to infections by unconventional viral pathogens. In immunodeficient children, for example, rotavirus can cause a protracted diarrhea with prolonged viral excretion, and in rare instances can disseminate systemically and
cause hepatic infection [Gilger, et al., 1992; Oshitani, et al., 1994]. A recent study from Malawi showed that rotavirus was detected less frequently in HIV-infected than HIV-uninfected children, and the clinical outcome of disease and immune responses to infection were similar in both groups of children [Cunliffe, et al., 2001]. In immunodeficient children, adenovirus infection can cause a disseminated infection of the lung, liver, bone marrow, heart, and brain and produce fulminant hepatitis [Krilov, et al., 1990]. Cytomegalovirus (CMV) is a common and potentially serious opportunistic gastrointestinal pathogen in HIV-infected persons. Colitis is the most common manifestation, although CMV can infect any part of the gastrointestinal tract [Grant, Section IV, Chapter 4 of this book].

**Prevention**

The immense disease burden of viral gastroenteritis underscores the need for effective prevention strategies. Endemic rotavirus disease is clearly the most important target for prevention, and efforts to develop rotavirus vaccines were initiated many years ago when it became apparent that improvements in hygiene and sanitation were unlikely to interrupt viral transmission [Bresee, et al., 1999]. A vaccine against rotavirus was licensed for the first time in the United States in 1998 but was withdrawn a year later following strong suspicion and evidence of its association with intussusception [Centers for Disease Control and Prevention, 1999; Murphy, et al., 2001; Offit et al., Section II, Chapter 13 of this book]. Despite this setback, efforts to develop other candidate vaccines are underway, and products currently in clinical trials may be available for use in the next few years. The role of other viruses, including caliciviruses, astroviruses, and adenoviruses in the etiology of severe endemic gastroenteritis needs to be better defined to determine whether these viruses should be targeted for prevention through vaccination.

For the prevention of epidemic viral gastroenteritis, efforts clearly need to be focused on caliciviruses. The epidemic spread of caliciviruses is facilitated by the low infectious dose (<100 viral particles), ability of the virus to survive at relatively high levels of chlorine and temperatures from freezing to 60°C, great genetic diversity, and lack of lasting immunity [Kapikian, et al., 1996]. Efforts to prevent calicivirus outbreaks currently focus on identifying and eliminating sources of contamination of food and water. Person-to-person spread of caliciviruses can be reduced by good hygiene practices but is often difficult to interrupt; consequently, outbreaks spread by this mode in institutional settings (e.g., nursing homes) often run their natural course and terminate when susceptible persons are exhausted.

**Treatment**

No specific antiviral therapy is recommended for childhood viral gastroenteritis, emphasizing the importance of distinguishing it from the selected forms of bacterial
and parasitic gastroenteritis that require treatment. Other than pertinent epidemiologic information (e.g., age of patient, history of travel, consumption of specific food items, immune status), certain clinical features of illness (e.g., incubation period, duration of illness) may provide etiologic clues but these features are not highly discriminating.

Standard therapy of viral enteric infections relies on maintenance of adequate hydration and electrolyte balance. Oral rehydration therapy (ORT) is the main treatment [Duggan, et al., 1992], and its efficacy has been confirmed in numerous trials worldwide and demonstrated by a substantial decline in the global mortality from diarrheal disease. In patients with severe disease or those who are unable to tolerate ORT, intravenous fluid therapy is recommended [see also Bass, Section I, Chapter 5 of this book].

Antimotility agents are not recommended [Desselberger, et al., 1999], but enkephalinase inhibitors that reduce hypersecretion but do not alter motility have been demonstrated to be effective in the management of childhood diarrhea [Salazar-Lindo, et al., 2000]. The role of other experimental therapies, including oral administration of immunoglobulin or probiotics, is still under investigation [Szajewska and Mrukowicz, 2001].

References

Ball JM, Tian P, Zeng CQ-Y, Morris AP, Estes MK (1996). Age-dependent diarrhea induced by a rotaviral nonstructural glycoprotein. Science 272:101-4.
Bern C, Martines J, de Zoysa I, Glass RI (1992). The magnitude of the global problem of diarrhoeal disease: a ten year update. Bull World Health Organ 70:705-14.
Bishop RF, Davidson GP, Holmes IH, Ruck BJ (1973). Virus particles in epithelial cells of duodenal mucosa from children with viral gastroenteritis. Lancet i:1281-3.
Bon F, Fascia P, Dauvergne M, Tenenbaum D, Planson H, Petion AM, Pothier P, Kohli E (1999). Prevalence of group A rotavirus, human calicivirus, astrovirus, and adenovirus type 40 and 41 infection among children with acute gastroenteritis in Dijon, France. J Clin Microbiol 37:3055-8.
Brandtzaeg P (1998). Development and basic mechanisms of human gut immunity. Nutr Rev 56:S5-18
Bresee J, Glass RI, Ivanoff B, Gentsch J (1999). Current status and future priorities for rotavirus vaccine development, evaluation, and implementation in developing countries. Vaccine 17:2207-22.
Centers for Disease Control and Prevention (1999). Intussusception among recipients of rotavirus vaccine, United States, 1998-1999. Morb Mortal Wkly Rep 48:577-81.
Chiba S, Nakata S, Numata-Kinoshita K, Honma S (2000). Sapporo virus: history and recent findings. J Infect Dis 181 (suppl 2):S303-8.
Coulson BS, Grimwood K, Masendycz P, Lund J, Mermelstein N, Bishop R, Barnes G (1990). Comparison of rotavirus immunoglobulin A coproconversion with other indices of rotavirus infection in a longitudinal study in childhood. J Clin Microbiol 28:1367-74.
Coulson BS, Grimwood K, Hudson IL, Barnes GL, Bishop RF (1992). Role of coproantibody in clinical protection of children during reinfection with rotavirus. J Clin Microbiol 30:1678-84.

Cunliffe NA, Gondwe JS, Kirkwood CD, Graham SM, Nhlane NM, Thindwa BDM, Dove W, Broadhead RL, Molyneux ME, Hart CA (2001). Effect of concomitant HIV infection on presentation and outcome of rotavirus gastroenteritis in Malawian children. Lancet 358:550-5.

Cunningham AL, Grohmann GS, Harkness J, Law C, Marriott D, Tindall B, Cooper DA (1988). Gastrointestinal viral infections in homosexual men who were symptomatic and seropositive for human immunodeficiency virus. J Infect Dis 158:386-91.

Desselberger U (1999). Rotavirus infections: guidelines for treatment and prevention. Drugs 58:447-52.

de Wit MA, Koopmans MP, Kortbeek LM, van Leeuwen NJ, Bartelds AI, van Duynhoven YT (2001). Gastroenteritis in sentinel general practices, The Netherlands. Emerg Infect Dis 7:82-91.

Duggan C, Santosham M, Glass RI (1992). The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy. Morb Mortal Wkly Rep 41(RR-16):1-20.

Fankhauser RL, Noel JS, Monroe SS, Ando TA, Glass RI (1998). Molecular epidemiology of “Norwalk- like viruses” in outbreaks of gastroenteritis in the United States. J Infect Dis 178:1571-8.

Flewett TH, Beards GM, Brown DW, Sanders RC (1987). The diagnostic gap in diarrhoeal aetiology. Ciba Found Symp 128:238-49.

Flewett TH, Bryden AS, Davies H (1973). Virus particles in gastroenteritis. Lancet ii: 1497.

Franco AA, Greenberg HB. Role of B cells and cytotoxic T lymphocytes in clearance of and immunity to rotavirus infection in mice (1995). J Virol 69:7800-06.

Gilger MA, Matson DO, Conner ME, Rosenblatt HM, Finegold MJ, Estes MK (1992). Extraintestinal rotavirus infections in children with immunodeficiency. J Pediatr 120:912-7.

Giordano MO, Martinez LC, Rinaldi D, Guinard S, Naretto E, Casero R, Yacci MR, Depetris AR, Medeot SI, Nates SV (1998). Detection of picobirnavirus in HIV-infected patients with diarrhea in Argentina. J Acq Imm Defic Syndr Hum Retrovirol 18:380-3.

Giordano MO, Martinez LC, Espul C, Martinez N, Isa MB, Depetris AR, Medeot SI, Nates SV (1999). Diarrhea and enteric emerging viruses in HIV-infected patients. AIDS Res Hum Retroviruses 15:1427-32.

Glass RI, Bresee J, Jiang B-M, Gentsch J, Ando T, Fankhauser R, Noel J, Parashar U, Rosen B, Monroe SS (2001). Gastroenteritis viruses: an overview. Novartis Found. Symp. 238:5-19.

Gonzalez GG, Pujol FH, Liprandi F, Deibis L, Ludert JE (1998). Prevalence of enteric viruses in human immunodeficiency virus seropositive patients in Venezuela. J Med Virol 55:288-92.
Gordon I, Ingraham HS, Korns RF (1947). Transmission of epidemic gastroenteritis to human volunteers by oral administration of fecal filtrates. J Exp Med 86:409-22.

Graham DY, Jiang X, Tanaka T, Opekun AR, Madore HP, Estes MK (1994). Norwalk virus infection of volunteers: new insights based on improved assays. J Infect Dis 170:34-43.

Gray JJ, Cunliffe C, Ball J, Graham DY, Desselberger U, Estes MK (1994). Detection of immunoglobulin M (IgM), IgA, and IgG Norwalk virus-specific antibodies by indirect enzyme-linked immunosorbent assay with baculovirus-expressed Norwalk virus capsid antigen in adult volunteers challenged with Norwalk virus. J Clin Microbiol 32:3059-63.

Greenberg HB, Clark HF, Offit PA (1994). Rotavirus pathology and pathophysiology. In: Ramig RF, ed. Rotaviruses. Berlin: Springer-Verlag, 255-83.

Grohmann GS, Glass RI, Pereira HG, Monroe SS, Hightower AW, Weber R, Bryan RT (1993). Enteric viruses and diarrhea in HIV-infected patients. N Engl J Med 329:14-20.

Johnson PC, Mathewson JJ, Dupont HL, Greenberg HB (1990). Multiple-challenge study of host susceptibility to Norwalk gastroenteritis in US adults. J Infect Dis 161:18-24.

Kaljot KT, Ling JP, Gold JWM, Laughon BE, Bartlett JG, Kotler DP, Oshiro LS, Greenberg HB (1989). Prevalence of acute enteric viral pathogens in acquired immunodeficiency syndrome patients with diarrhea. Gastroenterology 97:1031-2.

Kapikian AZ, Wyatt RG, Dolin R, Thornhill TS, Kalica AR, Chanock RM (1972). Visualization by immune electron microscopy of a 27 nm particle associated with acute infectious nonbacterial gastroenteritis. J Virol 10:1075-81.

Kapikian AZ, Estes MK, Chanock RM (1976). Norwalk group of viruses. In: Fields BN, Knipe DM, Howley PM, Chanock RM, Melnick JL, Monath TP, Roizman B, Straus SE, eds. Fields Virology. 3rd ed. Philadelphia: Lippincott-Raven, 1996: 783-810.

Koopmans M, Petric M, Glass RI, Monroe SS (1993). Enzyme-linked immunosorbent assay reactivity of torovirus-like particles in fecal specimens from humans with diarrhea. J Clin Microbiol 31:2738-44.

Krillov LR, Rubin LG, Frogel M, Gloster E, Ni K, Kaplan M, Lipson SM (1990). Disseminated adenovirus infection with hepatic necrosis in patients with human immunodeficiency virus infection and other immunodeficiency states. Rev Infect Dis 12:303-7.

Lundgren O, Peregriin AT, Persson K, Kordasti S, Uhrnoo I, Svensson L (2000). Role of the enteric nervous system in the fluid and electrolyte secretion of rotavirus diarrhea. Science 287:491-5.

Madeley CR, Cosgrove BP (1975a). 28 nm particles in faeces in infantile gastroenteritis. Lancet ii:451-2.

Madeley CR, Cosgrove BP (1975b). Viruses in infantile gastroenteritis (letter). Lancet ii:124.

Matson DO, O'Ryan ML, Herrera I, Pickering LK, Estes MK (1993). Fecal antibody
responses to symptomatic and asymptomatic rotavirus infections. J Infect Dis 167:577-83.
McNeal MM, Rae MN, Ward RL (1997). Evidence that resolution of rotavirus infection in mice is due to both CD4 and CD8 cell-dependant activities. J Virol 71: 8735-42.
Meeroff JC, Schreiber DS, Trier JS, Blacklow NR (1980). Abnormal gastric motor function in viral gastroenteritis. Ann Intern Med 92:370-3.
Miller MA, McCann L (2000). Policy analysis of the use of hepatitis B, Haemophilus influenzae type B-, Streptococcus pneumoniae-conjugate, and rotavirus vaccines in National Immunization Schedules. Health Econ 9:19-35.
Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, Zanardi LR, Setia S, Fair EL, LeBaron CW, Schwartz B, Wharton M, Livingood JR (2001). Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 344:564-72.
Murray CJ, Lopez AD (1997). Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 349:1436-42.
Offit PA (1996). Host factors associated with protection against rotavirus disease: the skies are clearing. J Infect Dis 174 (suppl 1):S59-64.
Osborne MP, Haddon SJ, Spencer AJ, Collins J, Starkey WG, Wallis TS, Clarke GJ, Worton KJ, Candy DCA, Stephen J (1988). An electron microscopic investigation of time-related changes in the intestine of neonatal mice infected with murine rotavirus. J Pediatr Gastroenterol Nutr 7:236-48.
Oshitani H, Kasolo FC, Mpabalwani M, Luo NP, Matsubayashi N, Bhat GH, Suzuki H, Numazaki Y, Zumla A, DuPont HL (1994). Association of rotavirus and human immunodeficiency virus infection in children hospitalized with acute diarrhea, Lusaka, Zambia. J Infect Dis 169:897-900.
Pang X-L, Honma S, Nakata S, Vesikari T (2000). Human caliciviruses in acute gastroenteritis of young children in the community. J Infect Dis 181 (suppl 2):S288-94.
Parrino TA, Schreiber DS, Trier JS, Kapikian AZ, Blacklow NR (1977). Clinical immunity in acute gastroenteritis caused by Norwalk agent. N Engl J Med 297: 86-9.
Qiao H, Nilsson M, Abreu ER, Hedlund K-O, Johansen K, Zaori G, Svensson L (1999). Viral diarrhea in children in Beijing, China. J Med Virol 57:390-6.
Rosen BJ, Fang Z-Y, Glass RI, Monroe SS (2000). Cloning of human picobirnavirus gene segments and development of an RT-PCR detection assay. Virology 277: 316-29.
Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E, Gutierrez M (2000). Racemadotril in the treatment of acute watery diarrhea in children. N Engl J Med 343:463-7.
Schmidt W, Schneider T, Heise W, Weinke T, Epple HJ, Stoffler-Melilicke M, Liesenfeld O, Ignatius R, Zeitz M, Riecken EO, Ullrich R (1996). Stool viruses, coinfections, and diarrhea in HIV-infected patients. J Acqu Imm Defic Syndr Hum Retrovirol 13:33-8.
Slutsker L, Ries AA, Greene KD, Wells JG, Hutwagner L, Griffin PM (1997).
Escherichia coli O157:H7 diarrhea in the United States: clinical and epidemiologic features. Ann Intern Med 126:505-13.

Szajewska H, Mrukowicz JZ (2001). Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebo-controlled trials. J Pediatr Gastroenterol Nutr 33:17-25.

Tompkins DS, Hudson MJ, Smith HR, Eglin RP, Wheeler JG, Brett MM, Owen RJ, Brazier JS, Cumberland P, King V, Cook PE (1999). A study of infectious intestinal disease in England: microbiological findings in cases and controls. Commun Dis Public Health 2:108-13.

Tucker AW, Haddix AC, Bresee JS, Holman RC, Parashar UD, Glass RI (1998). Cost-effectiveness analysis of a rotavirus immunization program for the United States. J Am Med Ass 279:1371-6.

Velazquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, Glass RI, Estes MK, Pickering LK, Ruiz-Palacios GM (1996). Rotavirus infections in infants as protection against subsequent infections. N Engl J Med 335:1022-8.

Wadell G, Allard A, Johansson M, Svensson L, Uhnoo I (1987). Enteric adenoviruses. Ciba Found Symp 128:63-91.

Yamashita T, Kobayashi S, Sakae K, et al. (1991). Isolation of cytopathic small round viruses with BS-C-1 cells from patients with gastroenteritis. J Infect Dis 164:954-7.

Yamashita T (1999). Biological and epidemiological characteristics of Aichi virus, as a new member of Picornaviridae [Japanese]. Uirusu 49:183-91.