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Viral Gastroenteritis
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I, 1. Viral causes of gastroenteritis

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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.

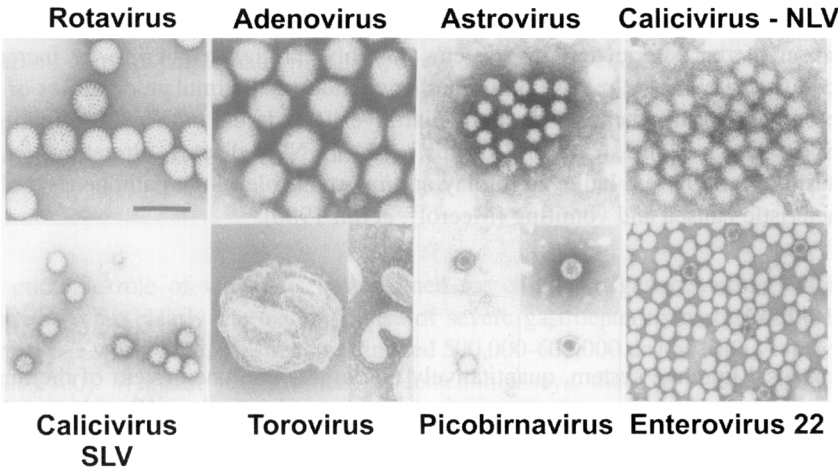

Fig. 1. Viral agents of gastroenteritis as seen by electron microscopy. Bar = 100 nm. (Reproduced with permission from Glass *et al.*, 2001)

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 2.5×10^{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.

Table 2

Recent studies demonstrating the role of enteric viruses in the etiology of acute gastroenteritis among children and adults in various countries.

	% children infected			% adults infected	
	France [Bon, *et al.*, 1999]	China [Qiao, *et al.*, 1999]	Finland [Pang, *et al.*, 2000]	England [Tompkins, *et al.*, 1999]	The Netherlands [de Wit, *et al.*, 2001]
	inpatients / outpatients (N = 414)	inpatients (N = 186)	community (N = 832)	community (N = 761)	community (N = 857)
Any virus	72	NA	60	NA	15
Rotavirus	61	56	31	8	5
Caliciviruses	14	8	30	9	7
Astroviruses	6	9	9	3	2
Adenoviruses	3	3	6	3	2

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].

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