A review of viral gastroenteritis

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Purpose of review

Since Kapakian first identified a virus in the stool of a patient with diarrhoea in 1972, many viruses have been described that cause diarrhoea directly or indirectly. It is now appreciated that viruses are the most common cause of diarrhoeal illness worldwide. Although bacteria and other pathogens cause significant numbers of gastroenteritis, it is the viruses that are dealt with in this review. The viruses responsible will be discussed individually.

Recent findings

Rotavirus remains the leading cause of diarrhoeal disease overall, with the newly designated calicivirus family causing the most outbreaks in the industrialized nations. As diagnostic techniques improve, however, the importance of astrovirus and other previously under-reported pathogens is becoming more apparent and the number of viruses associated with gastroenteritis continues to increase. The emergence of severe acute respiratory syndrome coronavirus, arguably the most important emerging infection of recent years and a cause of significant gastrointestinal disease, is also discussed.

Summary

No effective treatments have been developed for viral gastroenteritis. Current efforts are targeted at the development of suitable vaccines and the implementation of infection control measures.

Keywords

viral gastroenteritis, rotavirus, calicivirus, astrovirus, vaccine

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Abbreviations

ORF	open reading frame
PCR	polymerase chain reaction
SARS-CoV	severe acute respiratory syndrome coronavirus

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Introduction

Diarrhoeal diseases remain a leading cause of morbidity and mortality worldwide. Conservative estimates put the death toll at 4–6 million deaths per year, placing diarrhoeal diseases in the top five causes of death worldwide, with most occurring in young children in nonindustrialized countries. The majority of these infections are viral in origin. In industrialized nations viral gastroenteritis is one of the most common illnesses in all age groups, and an important cause of morbidity [1•–3•]. Surveys in the United States suggest nearly every American will have one or more episodes of viral gastroenteritis per year. Of these cases, approximately 450 000 adults and 160 000 children will be hospitalized, and more than 4000 deaths will occur [4,5].

The viruses will now be described.

Rotavirus

The wheel-like (Latin, *rota* = wheel) particles of rotavirus were first described as a human pathogen in 1973 [6], and are now classified as a genus within the family *Reoviridae*. The particles are 70 nm, nonenveloped icosahedral structures (see Fig. 1). An inner and outer capsid gives a double layer, surrounding a core containing the viral genome. The double-stranded RNA consists of 11 segments, which encode six viral capsid proteins (VP1, 2, 3, 4, 6 and 7) and six nonstructural proteins (NSP1–6). The outer capsid is mainly composed of two proteins, VP4 and VP7. VP4 is involved in attachment to cells and gives the spoke-like appearance of the rotavirus 'wheel', whereas VP7 gives the virus its smooth surface [7].

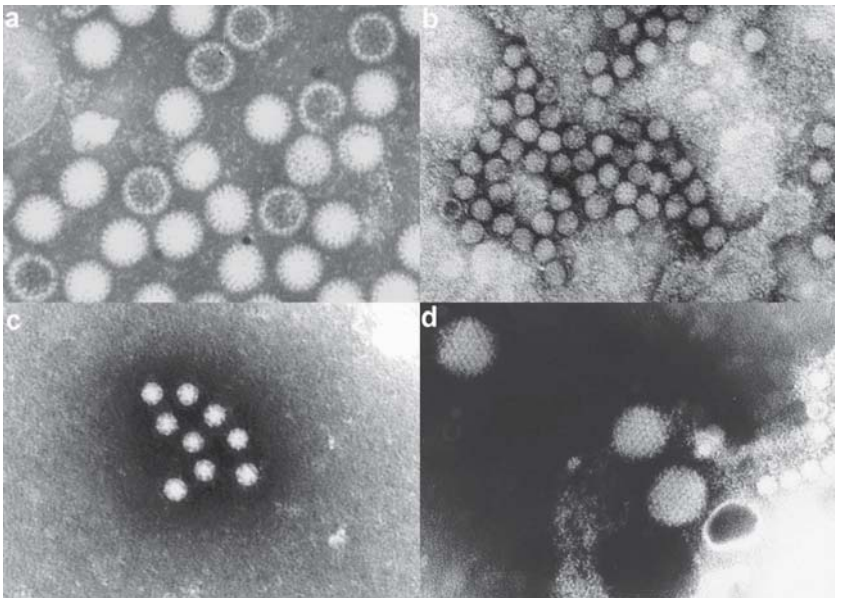
Rotaviruses are classified into seven serogroups (A–G) based upon the antigenic properties of VP6, an inner capsid protein, of which groups A, B, and C are human pathogens. Within the groups, viruses are classified into serotypes on the basis of differing outer capsid antigens. To date, 15 group A VP7 antigens (termed G types, G1—G15) and 20 VP4 antigens (termed P types, P1–P20) have been described [8••,9••].

Epidemiology

Rotavirus causes 600 000–875 000 deaths per year. The burden is most severe in the very young and in developing countries. In children under 5, rotavirus is responsible for over 2 million hospitalizations and up to 600 000 deaths per year [10]. It is also a significant cause of disease in industrialized countries, and proportionally

Figure 1. Negative stain transmission electron micrographs of stool samples containing viral particles

(a) Rotavirus, 75 nm diameter. Note the spoke-like components producing the wheel appearance. (b) Norovirus, 35–39 nm. Few distinguishing features are visible, unlike other caliciviruses, which may exhibit a 'Star of David' structure. (c) Astrovirus, 27–30 nm. Note the five or six-pointed star-like surface structure. (d) Adenovirus, 70–90 nm. Large nonenveloped icosahedral particles can be seen with associated 'dependent viruses' (small particles visible at the right of the image). Pictures courtesy of Dr G. Kudesia.



may account for a greater number of hospital admissions compared with that in non-industrialized countries [1•]. The vast majority of these infections are caused by group A rotavirus, however group B rotavirus is also responsible for significant outbreaks and may cause endemic disease in certain regions, for example China and Bangladesh [11,12•]. Group C rotavirus is known to cause sporadic disease and since its first description in the United States in 1995 has been described in other countries [13,14]. It may cause significant disease on its own or in mixed infection with group A virus where rotavirus is endemic [15]. Also, although most group A infections occur endemically, rotavirus can cause significant outbreaks [16•,17•].

Of the rotavirus group A serotypes, at least 10 G serotypes and eight P genotypes cause human infections. G1–4 are the most common G types found worldwide, and P[4] and P[8] are the most common P types found in association with them. G1P[8], G2P[4], G3P[8], and G4P[8] are the most common combinations globally [18•]. This pattern is seen in industrialized and non-industrialized countries, although mixed infections tend to be more commonly described in non-industrialized countries [19]. Table 1 illustrates the frequency of rotavirus G types isolated in several recent studies [20,21,22•,23•]. More unusual G types are becoming more common, especially G9 [21,22•,24]. G5, G8, and G10 types have been described in Brazil [25], G8 in Malawi [26], G12 in India [27•], and novel G6 serotypes in Hungary [28••].

It has been suggested that new serotypes of rotavirus have evolved to escape host immune surveillance. Because of this evolution, monitoring of the VP4 and VP7 antigens is essential to understand the genetic and molecular diversity of the virus at a regional and global level in order to target the correct proteins for vaccine development [23•].

Pathogenesis and immunity

Rotavirus spreads from person to person, mainly by faeco-oral transmission. Hypotheses of the mechanism of diarrhoea include a reduction in the absorptive surface and impaired absorption due to cell damage, enterotoxigenic effects of NSP4 (a rotavirus protein), and stimulation of the enteric nervous system [9••]. Detectable rotavirus antigenaemia and viraemia suggests that rotavirus escapes from the intestinal tract. Access to the bloodstream may be via transport through M cells, which overlie Peyer's patches [29••].

Clinical manifestation

Most rotavirus infections occur in children aged 6 months to 2 years, usually during winter months. In all age groups a 2–3-day prodrome of fever and vomiting is followed by non-bloody diarrhoea. Typically, there are up to 10–20 bowel movements per day, and as a consequence the infection can cause severe dehydration. In studies on healthy adults, the diarrhoea followed 2–6 days after ingestion of rotavirus particles and continued for 1–4 days. The associated symptoms in adults are summarized in Table 2.

Table 1. Summary of the rotavirus G types identified in four large studies in different countries

	G1 (%)	G2 (%)	G3 (%)	G4 (%)	G9 (%)	Other (%)	Mixed (%)	Not typed (%)	Total patients
Australia	58.1	7.1	0.5	1.2	9.6	0		23.4	2843
India	38.1	11.1	0	3.2	0	0	31	16.7	126
Vietnam	68.7	12.3	0.6	15.4	0.5	0	2.0	0.5	889
S. Korea	28.3	1.5	2.9	40.9	0	0	13.7	12.7	205

Data from [20,21,22•,23•].

Table 2. Incidence of symptoms in healthy adult volunteers after rotavirus ingestion

	(%)
All symptoms	39
Diarrhoea	31
Nausea	22
Anorexia	21
Temperature $>37.2^{\circ}C$	18
Headache	16
Malaise	15
Cramping legs	15
Chills	11
Vomiting	9

Adapted from Anderson and Weber [8••].

Patients with immunodeficiency may suffer with more severe or more prolonged diarrhoea. This has been described in the setting of HIV [30,31], solid organ transplantation [32,33], bone marrow transplantation [34], and natural killer cell deficiency [35]. A large study of diarrhoea in Malawian children, however, found no difference in clinical disease between HIV-infected and non-infected patients [36].

Increasingly rotavirus is described from extra intestinal sites including the central nervous system, liver, spleen, and kidney [29••,37••].

It is known that local intestinal immunity gives protection against successive infection, although the exact immunological mechanisms remain unclear and beyond the scope of this review.

Diagnosis

The method of choice for diagnosis of rotavirus is by polymerase chain reaction (PCR) of the stool. This is more sensitive than microscopy and serological methods, and also less time-consuming. Single-step techniques also prevent contamination from other samples [38•]. Novel methods for typing, including microarrays, have been shown to be of use [39•,40••].

Treatment

Various agents have been shown to be partially effective in rotavirus diarrhoea treatment [41•]. The mainstay of management though remains supportive and directed at restoring normal physiological function. Oral fluids and supplementary nutrition in the malnourished patient remain the basis of therapy, with parenteral fluids if required [42]. Immunoglobulin has been used in chronic cases and in the immunosuppressed [43], and its use in neonates was recently reviewed [44••]. Antiperistaltic or antisecretory drugs should be avoided as they can cause serious side effects in children.

Prevention

Since the withdrawal of the first licensed rotavirus vaccine (the oral rhesus-human tetravalent vaccine released in 1998), no other products have been licensed [45]. However, because of the large burden of rotavirus diarrhoea, vaccine research continues [46•,47•]. There is concern over the effectiveness of future vaccines, however, because of the high polymorphism of the virus, and the difficulty of reaching remote populations [48].

Caliciviruses

Kapikian *et al.* [49] first described the 'prototype' calicivirus in 1972 during an outbreak of gastroenteritis in a school in Norwalk, Ohio. Due to an inability to culture the virus, further classification and epidemiological study faltered until recently, when sensitive molecular techniques became available [50•,51]. Four genera are now described, each sharing features under electron microscopy (see Fig. 1). These include noroviruses, previously denoted as 'small round structured viruses' or 'Norwalk-like viruses', and sapoviruses, previously denoted as sapporo-like viruses [52••]. It is the noroviruses that cause the most disease and are discussed here in detail.

Noroviruses are a genetically diverse group of single-stranded RNA viruses. There are four genogroups: genogroup I, II, and IV (GI, GII, and GIV) infect humans, and genotype III (GIII) only affect cattle. The groups are further classified according to amino acid sequences from the capsid gene, and the location where the virus was first described, for example GI/1 (Norwalk virus), GII/4 (Bristol virus).

Epidemiology

Noroviruses are the most common cause of outbreaks of nonbacterial gastroenteritis and it is estimated that they

are responsible for 68–80% of all outbreaks of gastroenteritis in industrialized countries. In the United States, noroviruses accounted for 93% of outbreaks of viral gastroenteritis examined over a 3-year period [53]. The emergence and detection of new strains often coincide with the increase in norovirus outbreaks [54•]. When these outbreaks occur, thousands of persons can be infected, causing the closure of facilities and businesses [55•,56]. It is for this reason that noroviruses have since been described as being the most important cause of viral gastroenteritis worldwide.

During the 1990s, GII was the most common type identified in outbreaks [54•,57•]. Interestingly it was noted that in cruise ship settings genogroup I noroviruses were more common than in the hospital outbreaks. Also outbreaks on cruise ships were more common in the summer months than in winter [58•].

Clinical manifestation

Norovirus infections result from ingestion of viral particles, which includes possible airborne transmission [59•]. After a short incubation period (12–48 h), symptoms of nausea, vomiting, and diarrhoea follow. The illness is usually mild and self-limiting, but has a high secondary attack rate, resulting in high rates of transmission and large outbreaks. The seasonal periodicity of different norovirus strains has been demonstrated [60•]. The immunology and resistance to norovirus infection are reviewed in a recent *Nature* paper [61••].

Diagnosis

Diagnosis is by electron microscopy, immune transmission electron microscopy, ELISA, and PCR. All four methods are useful for epidemiological studies, but at least two should be combined in individual diagnoses [62•]. PCR is valuable in both the outbreak and sporadic case settings, as it is both rapid and sensitive [63,64•].

Vaccines and prevention

The disease burden for rotavirus gastroenteritis is well evaluated. As the clinical and socioeconomic burden of norovirus infection becomes more apparent, so does the rationale for developing a vaccine [65]. The use of oral recombinant norovirus-like particles is promising and the use of a mucosal adjuvant for increased immunogenicity is planned [66].

Treatment

There is no specific treatment for calicivirus infections. Optimum management of a norovirus outbreak must include the rapid diagnosis of norovirus. In the hospital setting prompt implementation of infection control measures, staff restrictions, the cleaning of surfaces with an effective disinfectant, and ward closure can limit the spread of infection [55•].

Astroviruses

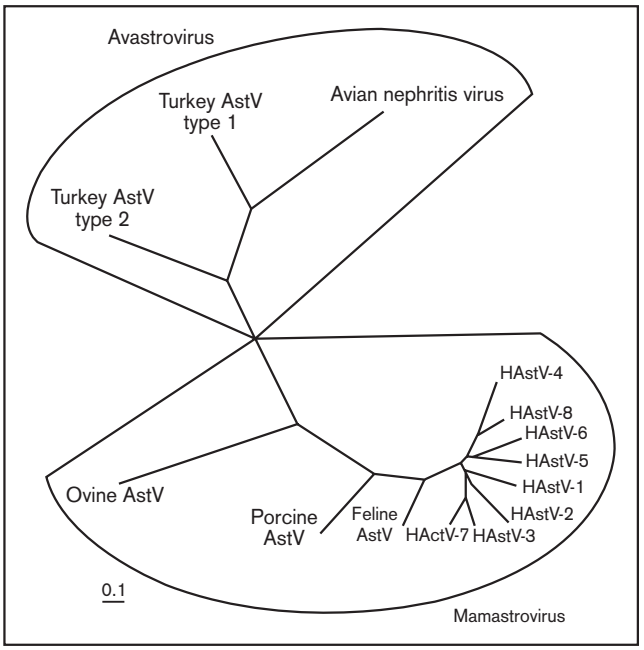
The *Astroviridae* family is divided into two genera: *Mamastrovirus*, which encompasses human astroviruses and animal astroviruses; and *Avastrovirus*, the avian astroviruses. See Fig. 2 [67•].

Astroviruses were initially described as 28–35 nm diameter nonenveloped particles, appearing as a five or six-pointed star (Latin, *astron* = star; see Fig. 1). The astrovirus genome is a single-stranded positive sense RNA molecule containing three open reading frames (ORFs): ORF1a, ORF1b, and ORF2. ORF2 encodes the capsid precursor protein used to classify astroviruses [68].

Epidemiology

Although not as important as other causes, with regards to disease severity, astroviruses probably cause more cases of gastroenteritis than noroviruses [69]. Human astrovirus 1 remains the most prevalent serotype, although detection of others is increasing due to newer

Figure 2. A phylogram of open reading frame 2 of astroviruses



Phylogram includes human astrovirus (AHAstV) serotypes 1–8, feline astrovirus (AstV), porcine AstV, ovine AstV, turkey AstVs, and avian nephritia virus (GenBank Acc# L23513, NC_002470, AF141381, Z33883, U15136, Z46658, AF248738, NC_002499, AF056197, Y15938, NC_002469, AF206663, Y15936, NC003790). Branch points of the resulting tree had a confidence level of $P < 0.01$. This is an unrooted tree. Distances can be estimated using the scale bar (number of nucleotide substitutions per site). Two distinct dusters were recently accepted as two genera by the International Committee on Taxonomy of Viruses, namely Mamastrovirus and Avastrovirus. The Mamastrovirus genus includes all human astrovirus strains, feline astrovirus, porcine astrovirus, and ovine astrovirus. Avastrovirus includes turkey astroviurses and avian nephritis viurs (personal communication, D. Mitchell).
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assays rather than the emergence of new types [70,71•]. Mixed infection with rotavirus is often seen.

Clinical manifestation

Transmission of astrovirus is by ingestion of faecal particles. The diarrhoea is of shorter duration and is less severe than that caused by other enteric viruses and other symptoms, for example fever and vomiting occur less frequently. Young children are more commonly affected and have more severe disease [72]. The virus may be shed in stools for up to 2 weeks, although this can be more prolonged in immunodeficient patients. More severe symptoms are seen in immunodeficient patients and in cases due to serotype 3 [73•].

Diagnosis

Only 10% of astrovirus particles have the typical 'star' appearance, making definite identification difficult by microscopy [74]. PCR of the stool is the most sensitive diagnostic method. An interesting development is the use of a multiplex PCR to diagnose several enteric pathogens, including astrovirus, caliciviruses, and enteric adenoviruses [75•].

Treatment

Astrovirus infections usually resolve without specific treatment. There is currently no vaccine for astrovirus.

Enteric adenoviruses

At least 51 adenovirus serotypes (Ad1–51) in six subgenera (A–F) have been described in humans [76]. Although diarrhoea may be a feature of infection by other adenoviruses, for example Ad3 and Ad7, most adenovirus gastroenteritis is caused by the so-called enteric adenoviruses, Ad40 and Ad41, which are members of subgenus F (see Fig. 1).

Up to 15% of diarrhoea is caused by adenoviruses [57•,77•,78–80].

Clinical manifestation

Adenovirus causes infection throughout the year, predominantly in young children. The incubation period of 8–10 days is longer than in other enteric viruses, as is the duration of diarrhoea. The illness is usually mild and self-limiting but can be persistent and severe in the immunosuppressed, causing specific adenovirus colitis in HIV-infected patients [31,81].

Diagnosis

Diagnosis is usually by ELISA and immune electron microscopy. Serotypes can be identified by neutralization and haemagglutination inhibition assays, restriction endonuclease analysis, or PCR. The latter is quicker and more sensitive. Recently, a fibre-based PCR was used for type-specific identification of adenovirus [82].

Coronaviridae

Until 2002, the coronavirus family had been thought of only in the context of the common cold. The viruses HCoV-OC43 and 229E cause up to a third of coryzal illnesses in humans, although occasionally they cause gastroenteritis in children in developing countries and the immunosuppressed, for example in HIV infection [83]. This changed when the severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in the Guangdong province of China, an event well described in the literature [84••,85•,86••,87••].

SARS-CoV also causes significant gastrointestinal disease. In the initial Hong Kong outbreak, a total of 38.4% of SARS-CoV infected patients developed diarrhoea during the first 3 weeks of admission, and some presented with a gastrointestinal illness only [88••]. SARS-CoV also appears to show tropism for the bowel, where it actively replicates in the absence of inflammation. The diarrhoea is possibly related to toxins and proteins released during viral replication within enterocytes. Where faeco-oral transmission was thought to have occurred, such as in the well documented Amoy Gardens outbreak, the proportion of patients developing diarrhoea was much higher, a possible reflection of the mode of spread [89••].

Compared with other pathogens in this review, the disease burden of SARS-CoV is small. The diarrhoea is usually mild and no deaths have been attributed to gastrointestinal disease. However, other issues such as the rapid global spread of this emerging pathogen and management of future outbreaks are very important. Viral shedding in the stool during the first few days of illness is at a low level, therefore early use of isolation of probable cases (which may include patients with gastroenteritis with possible contact with SARS-CoV) would probably be effective in preventing further spread by the faecal route [90•,91]. Viral particles have been detected in the stool up to 73 days after the onset of symptoms.

Routine collection and testing of stool specimens of probable SARS patients may help in the early detection of SARS-CoV infection, as they have the highest yield for coronavirus detection by PCR and collection procedures for stool specimens are less likely to transmit infection to health care workers than other methods [92••,93•]. PCR methods, in particular real-time PCR, have the highest specificity and sensitivity compared with tissue culture and serological methods [94,95•].

Toroviruses, also within the *Coronaviridae* family, are similar in appearance to the crown-like coronaviruses but often have a donut-shaped structure within the particle (Latin, *torus* = root). They are also known to cause gastrointestinal disease, more frequently in immunocompromised persons [96,97].

Other viruses causing gastroenteritis

Human parechovirus 1 causes mild gastrointestinal and respiratory disease [98]. Parechoviruses were previously designated as echoviruses 22 and 23 and classified within the enterovirus genus of the *Picornaviridae* family. These RNA viruses are not well studied, although it is known that replication is significantly different from other picornaviruses [99•]. Recently a third serotype has been described causing diarrhoea and transient paralysis [100]. Ljungan virus, a newly identified virus of rodents, shares a number of molecular features with the human parechoviruses, raising important questions about the evolution of parechoviruses and their introduction into the human population [101].

Picobirnaviruses are part of the *Birnaviridae* family and have recently been implicated as a cause of gastroenteritis in the immunosuppressed, including HIV patients [102]. Their role in the nonimmunosuppressed is not clear and requires further study [103,104].

Other viruses that cause gastrointestinal disease cannot be covered within the scope of this article. These include cytomegalovirus and herpes simplex virus, which cause disease in the immunosuppressed (e.g. in HIV-infected patients), and HIV itself may cause diarrhoea and a chronic enteropathy.

Conclusion

Viral gastrointestinal infections remain a significant cause of morbidity and mortality worldwide. Effective pharmaceutical treatments are lacking, however, and guidelines from the 1980s remain the basis for our current management of such patients. The search for effective immunization against these viruses should be a priority and emphasis must be placed on appropriate infection control methods in an effort to break the cycle of transmission in both endemic and outbreak/epidemic settings. The supply of clean water to the world's population is as important now as it ever has been.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

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