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Viral gastroenteritis

Ulrich Desselberger

Abstract

This article reviews the virology, immunology and epidemiology of the most common viral causes of acute gastroenteritis (rotaviruses, human caliciviruses, astroviruses, enteric adenoviruses). Clinical symptoms range from mild diarrhoea to life-threatening dehydration, and rotavirus disease is a major cause of childhood mortality, mainly in developing countries. The diagnosis, treatment and preventive measures are reviewed. Uncommon viral causes of acute gastroenteritis and viruses causing gastroenteritis in immunodeficient patients are also discussed. Two live attenuated rotavirus vaccines (Rotarix^{RTM}, RotaTeq^{RTM}) have been licensed in >100 countries since 2006 and used in universal mass vaccination (UMV) programmes. In addition, a new rotavirus vaccine was licensed in India in 2015 for UMV. Although rotavirus vaccines are highly effective in industrialized countries, they are less so in low-income countries of sub-Saharan Africa and South-East Asia. Vaccines against human norovirus disease are under development. Major progress has recently been made in basic research on rotaviruses and human caliciviruses.

Keywords Acute viral gastroenteritis; astrovirus; enteric adenovirus; human calicivirus; MRCP; norovirus; rotavirus; rotavirus vaccine; sapovirus

Introduction

Acute gastroenteritis with vomiting is easily recognized as a clinical entity but can be caused by very different agents (viruses, bacteria, parasites) or can have a non-infectious cause. [Table 1](#) lists viruses found in the human gut that have been recognized as:

- common causes of diarrhoea and vomiting in humans
- uncommon causes or not a cause of diarrhoea and vomiting in humans
- causes of diarrhoea in immunodeficient individuals.

This article discusses the major groups of viruses that commonly cause gastroenteritis in humans.

The viruses

Rotaviruses,¹ caliciviruses, astroviruses and enteric adenoviruses are the principal virus families involved. Their size, particle and genome structure, classification and epidemiological significance are summarized in [Table 2](#).

Rotaviruses

These are a major cause of infantile gastroenteritis worldwide.

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Key points

- Rotaviruses, caliciviruses (noroviruses, sapoviruses), astroviruses and enteric adenoviruses are major causes of acute gastroenteritis in infants and young children worldwide
- Gastroenteritis viruses occur endemically and regularly cause outbreaks or major epidemics
- Since 2006, two live attenuated rotavirus vaccines have been licensed in >100 countries and shown to be effective in reducing severe disease and mortality. Candidate norovirus vaccines are under development
- Recent research developments will enable innovative approaches in basic and translational research into gastroenteritis viruses

Structure: rotaviruses comprise an inner core containing a genome of 11 segments of double-stranded RNA and the transcription/replication and capping enzyme complex, a middle layer (inner capsid) consisting of viral protein 6 (VP6), and an outer layer made of VP7 and VP4, the latter protruding as spikes.¹

Classification: rotaviruses are a genus of the *Sedoreovirinae* subfamily in the *Reoviridae* family, and are routinely classified according to the immunological reactivities and genomic sequences of three of their structural components. Based on cross-reactivities and sequence diversities of VP6, at least nine groups/species (A–H/I) are distinguished.

The surface proteins VP4 and VP7 elicit type-specific neutralizing antibodies. Accordingly, for group A rotaviruses, which cause most human infections, a dual-type classification system has been established, differentiating G types (VP7-specific, 'G' derived from 'glycoprotein') and P types (VP4-specific, 'P' derived from 'protease-sensitive protein'). At present, 27 G types and 35 P types have been described, of which at least 11 G and 11 P types have been found in humans. More recently, genotype classification of the other nine RNA segments has been developed, permitting the detailed study of the evolution and transmission pathways of these viruses.

Replication and pathogenesis: rotaviruses replicate in mature epithelial cells at the tips of the villi in the small intestine. After virus adsorption to sialic acid, human histo-blood group antigens and various co-receptors, viral replication takes place, first in cytoplasmic inclusion bodies termed 'viroplasm', followed by maturation in contact with the endoplasmic reticulum. Mature particles are released from cells by lysis.¹ Rotavirus replication in the gut is rapid and reaches high titres (up to 10¹¹ virus particles/ml faeces at the peak of acute diarrhoea) within a short time.

The diarrhoea arises from epithelial necrosis and atrophy, leading to reduced absorption of carbohydrates and an increased osmotic gradient in the gut lumen. There is also a component of hypersecretion contributing to the diarrhoea. The rotavirus non-

Viruses infecting the human gut

Common causes of diarrhoea and vomiting^a

- Rotaviruses (11–68%)
- Caliciviruses (noroviruses, sapoviruses) (1–25%)^b
- Group F adenoviruses (1–10%)
- Astroviruses (1–5%)

Uncommon causes of diarrhoea and vomiting or asymptomatic infection

- Kobuviruses (including Aichivirus)
- Enteroviruses
- Orthoreoviruses
- Adenoviruses (other than group F)
- Toroviruses
- Coronaviruses (including SARS CoV)
- Parvoviruses (including bocavirus)

Causes of diarrhoea in immunodeficient individuals^c

- HIV
- Cytomegalovirus
- Herpes simplex virus
- Picobirnaviruses
- Adenoviruses types 42–47 (often systemic)

Viruses other than those commonly causing diarrhoea are seen sporadically; on average, viruses represent about one-third of all microbial causes of childhood diarrhoea.

SARS CoV, severe acute respiratory syndrome coronavirus.

^a Figures in parentheses are detection ranges in various surveys.

^b Most common cause of outbreaks.

^c In addition to common causes of diarrhoea and vomiting.

Table 1

structural protein 4 has various functions and acts as a viral enterotoxin.¹

Immune response: primary rotavirus infection leads to a serotype-specific humoral immune response with initially monotypic protection. During the first 2 years of life, children are repeatedly infected with rotaviruses of various types, resulting in a more complex immune response that seems to provide partial

heterotypic protection. Rotavirus-specific secretory antibodies of immunoglobulin A subclass in stool or serum have been identified as an important correlate of protection.²

Caliciviruses

Noroviruses (previously termed ‘Norwalk-like viruses’) and sapoviruses (previously termed ‘Sapporo-like viruses’) are the two (of five) genera of the *Caliciviridae* family that infect humans. The human noro- and sapoviruses are classified into 5–6 genogroups (I–VI), each group containing 1–19 different genotypes. Noroviruses of different genotypes co-circulate, but genotype II-4 noroviruses predominate worldwide. Genetic recombination among both norovirus and sapovirus strains is not infrequent.

These viruses were first recognized as a cause of human gastroenteritis outbreaks in the 1960s and are now considered the most important cause of non-bacterial gastroenteritis outbreaks and epidemics worldwide. In the UK and elsewhere, calicivirus outbreaks are common in hospital settings, care homes, etc. Human infections with caliciviruses elicit virus-specific immune responses, although these do not seem to provide full protection from subsequent infections.

Astroviruses

Astroviruses are members of the *Astroviridae* family and have a characteristic appearance when viewed by electron microscopy. Within the *Mamastrovirus* genus, two genogroups and a total of 19 genotypes have been differentiated, with human serotypes Ast1–Ast8 being classified as members of genogroup I. Eight different serotypes/genotypes have been distinguished; serotype 1 is most common. Little is known about immunity conveyed after astrovirus infection or the relative cross-protective effect of the immune response on reinfection with heterotypic strains.

Adenoviruses

Enteric adenoviruses of subgroup F (serotypes 40, 41) of the *Adenoviridae* are a less common cause of diarrhoea in infants and small children. They replicate in the cell nucleus and cytoplasm. Some adenovirus proteins inhibit apoptosis; others decrease the expression of host cell proteins, for example, major histocompatibility complex class I antigens on the surface of

Characteristics of viruses that commonly cause acute gastroenteritis in humans

Virus (family)	Size and structure	Genome composition	Classification	Epidemiology
Rotaviruses (<i>Reoviridae</i>)	75 nm, triple-layered, wheel-shaped	11 segments of dsRNA totalling 18.5 kb	Groups A–H Within group A subgroups, G and P types Genotypes of all segments	Endemic in children worldwide, winter outbreaks in temperate climates, small epidemics in the elderly
Caliciviruses (<i>Caliciviridae</i>)	About 30 nm, surface cup-shaped	ssRNA, 7.7 kb	Two genera infecting humans: noroviruses, sapoviruses	Epidemics in humans of all age groups
Enteric adenoviruses (<i>Adenoviridae</i>)	About 70 nm, icosahedral	dsDNA, 36 kb	Group F serotypes 40, 41	Endemic in children
Astroviruses (<i>Astroviridae</i>)	About 30 nm, star-like appearance	ssRNA, 6.8 kb	Two genogroups, 19 genotypes	Epidemics in children and adults

ds, double-stranded; ss, single-stranded.

Table 2

infected cells, thereby reducing susceptibility to adenovirus-specific cytotoxic T cells. A serotype-specific humoral immune response provides homotypic protection.

Epidemiology

Rotaviruses

Infections occur endemically worldwide, in 2013 causing >200,000 deaths in children aged <5 years, mainly in low-income countries of sub-Saharan Africa and South-East Asia. The epidemiology of these infections is complex. There is a strict winter peak in temperate climates, but in tropical and subtropical regions infections occur throughout the year. Transmission is mainly by the faeco-oral route. Nosocomial infections occur on infant and paediatric wards and are difficult to eradicate.

Group A rotaviruses of different G and P types co-circulate in different populations within a geographical location, varying over time. Types G1–G4 and G9 represent >90% of co-circulating strains in temperate climates, but other G types (e.g. G5, G8, G10, G12) are increasing and may even become most prevalent, particularly in tropical and subtropical areas.

The young of many mammalian species harbour rotaviruses of diverse genotypes and have been found to act as reservoirs for human infections.¹ Most human infections are caused by group A rotaviruses. However, group B rotaviruses were established as the cause of acute gastroenteritis outbreaks in children and adults in China in the 1980s, and recently in Calcutta, India and other South-East Asian countries. Group C rotavirus infections are associated with isolated cases and small outbreaks of diarrhoea in humans.¹

Noroviruses

Norovirus infections exhibit a winter peak, and the associated clinical entity has become known as ‘winter vomiting disease’. Age-related seroprevalence surveys have shown that many infections with noroviruses occur in the young and are often inapparent. About 50% of children have been infected by the age of 2 years. It is now accepted that the incidence of infection with noroviruses and sapoviruses is largely underestimated; with the advent of rotavirus vaccination (see below), noroviruses are now becoming the main cause of acute gastroenteritis in children.

Norovirus disease outbreaks result from the ingestion of contaminated food (oysters, green salad) or water, although person-to-person spread is the predominant mode of transmission. Such outbreaks occur in both children and adults in recreational camps, hospitals, nursing homes, schools and cruise ships. Genetic and antigenic diversity arise through the accumulation of point mutations and the selection of variants through evolutionary pressure likely to be exerted by short-term herd immunity.

Astroviruses

These cause both endemic infections and food-borne outbreaks. Seroprevalence surveys have shown that individuals can become infected by more than one serotype.

Clinical features

The onset of acute viral gastroenteritis follows an incubation period of 1–2 days, with watery diarrhoea lasting 4–7 days, vomiting and varying dehydration. Fever is not common. As a rule, the duration of diarrhoea after infection with norovirus is shorter than after infection with rotaviruses or enteric adenoviruses.

Infection can be accompanied by abdominal cramps, headache, myalgia and projectile vomiting, which are regarded as typical of norovirus infection. After rotavirus infection, all severities of clinical symptoms are seen. The outcome depends on viral pathogenicity factors and on the host’s immune status. Inapparent infections can occur, particularly in neonates. Although rotavirus infection is often accompanied by respiratory symptoms, there is no strong evidence that rotaviruses replicate in the respiratory tract. Extraintestinal spread of rotaviruses has been reported and can result in viraemia or, very rarely, central nervous system disease (meningitis).

Chronic gut infections with rotaviruses, adenoviruses, noroviruses, sapoviruses and astroviruses have been seen in immunocompromised children. Chronic gut infections with human cytomegalovirus, adenoviruses of new serotypes (types 42–47) and picobirnaviruses have been reported in HIV-infected patients with AIDS-defining illnesses.

Diagnosis

The diagnosis of rotavirus, astrovirus and enteric adenovirus infections is relatively easy because large numbers of particles are produced and shed during the acute phase of the illness. Noroviruses and sapoviruses replicate to lower concentrations and for shorter periods.

Diagnosis is by electron microscopy of negatively stained specimen suspensions (‘catch-all method’), by passive particle agglutination tests, by virus-specific enzyme-linked immunosorbent assay and, more recently, by viral genome detection using polymerase chain reaction (PCR) analysis for enteric adenoviruses and reverse transcription PCR for rotaviruses, calciviruses and astroviruses. Molecular methods of diagnosis have now become the ‘gold standard’ in clinical virology.

Management

Treatment is mainly by oral or, in more severe cases, intravenous rehydration. In tropical areas where rotavirus infections are associated with high mortality, standard formulas of oral rehydration fluid are recommended by the World Health Organization (WHO) and widely used. Otherwise, treatment is symptomatic. Use of antimotility drugs is not advised in children, although there have been recent promising developments in the use of drugs with antisecretory activity, such as racecadotril. There are no specific antiviral chemotherapeutic agents in clinical use.

Outbreaks of nosocomial rotavirus infections are common in children on hospital wards and in day-care centres. Outbreaks of diarrhoea and vomiting caused by noroviruses occur in children and adults following banquets, on cruise ships, and in cafeterias, schools, hotels and fast-food restaurants. Outbreak control measures focus on interruption of person-to-person transmission, removal of sources of infection (food, water, food-

handlers), measures to improve environmental hygiene and disinfection of locations where the outbreak occurred.

Vaccine development

Development of vaccines against viral gastroenteritis has been directed mainly towards rotaviruses, which are a major cause of gastroenteritis and high childhood mortality in developing countries.

A live attenuated, rhesus rotavirus-based, human reassortant quadrivalent vaccine eliciting immunity to human rotavirus strains G1–G4 was found to protect significantly against severe disease, including dehydration. It was given US Food and Drug Administration approval for universal use in the USA in August 1998, and 1.5 million doses were used between September 1998 and July 1999. However, a Vaccine Adverse Events Reporting System found gut intussusception to be a rare complication, epidemiologically correlated with vaccination, particularly on days 3–7 after the first vaccination. The pathogenesis of this association is not clear. Although the vaccine-attributable risk of intussusception was considered very low in recent studies (<1/10,000), the recommendation for use of this vaccine in the USA was withdrawn in October 1999, and it was taken off the market by the manufacturer.¹

In the search for alternative vaccines, two further live attenuated oral rotavirus vaccines have been developed, with different underlying concepts. Pentavalent vaccine (RotaTeq^{RTM}) contains human antigens G1–G4 and P[8] in mono-reassortant viruses on a bovine rotavirus (WC3 strain) genetic backbone; it aims to elicit type-specific antibodies against all the rotavirus types recognized to circulate most frequently.

The rationale of the monovalent vaccine (Rotarix^{RTM}), an attenuated human G1P[8] strain, is based on two clinical observations. First, cross-protection is accumulated through successive natural infections, and rotavirus disease can be prevented by repeated natural infection. Second, vaccination with one rotavirus type can provide protection, even if subsequent infections are caused by rotaviruses of a different type. It should be noted that, despite considerable work, the exact correlates of protection against rotavirus disease are still not determined.²

Both vaccines have been found to be effective and safe. They have now been licensed for sale in >100 countries, and in many of these universal mass vaccination (UMV) against rotavirus disease as part of childhood vaccination schemes has been initiated. In the USA, a distinct decline in clinic visits and hospital admissions for rotavirus disease has been noted. Clinical trials with the new vaccines in developing countries, where they are most needed, have shown a decreased efficacy in preventing severe rotavirus disease for reasons that are not clear; however, because of the high rotavirus-associated mortality in these countries, the WHO decided in 2009 to recommend rotavirus vaccination worldwide.

As recorded in the USA, in most developed countries where UMV programmes against rotavirus disease have been introduced, a significant decrease in rotavirus-associated diarrhoea

requiring medical attention or hospitalization has been observed. In Europe, UMV against rotavirus disease is being carried out in Belgium, Finland, Luxemburg, Austria, several states in Germany and recently the UK. There will be intense post-marketing surveillance in order to determine the impact of the vaccine and to monitor the emergence of novel rotavirus strains. A new rotavirus vaccine was licensed in India in 2015 for UMV.

As the licensed rotavirus vaccine contains live, attenuated viruses, attention is focused on the development of virus-like particles (obtained from baculovirus recombinant co-expressed rotavirus proteins), enhancement of rotavirus immunogenicity by micro-encapsulation, DNA-based, and possibly 'edible' preparations as candidate vaccines. Combinations of vaccination with live attenuated and replication-incompetent vaccines are also being considered.

So far, no vaccines against other viruses causing gastroenteritis in humans have been licensed. Candidate vaccines specific for norovirus genotype II-4 and other genotypes are under development.³

Future research questions and needs

Recently, several exciting developments have occurred in research on gastroenteritis viruses:

- Human intestinal enteroids (3D arrangements of differentiated intestinal tissue) have been adapted to growth *in vitro* and shown to support the replication of rotaviruses and human noroviruses.^{4,5} This will permit various studies on pathogenesis and host specificity.
- For rotaviruses, a plasmid only-based, helper virus-free and fully tractable reverse genetics system has been developed (see Kanai *et al* in Further reading), which will open many new areas of basic and translational research, as happened for other RNA viruses when reverse genetics system became available. There will be a good chance of the development of improved rotavirus vaccines. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

Question 1

A 10-month-old girl presented with acute onset of watery diarrhoea and vomiting.

Which of the following investigations has the highest sensitivity and specificity of detecting the causative agent?

- A Electron microscopy
- B Enzyme linked immunosorbent assay
- C Reverse transcription-polymerase chain reaction or polymerase chain reaction
- D Passive particle agglutination test
- E Culture on blood agar plates

Question 2

Outbreaks of viral gastroenteritis cause considerable disruption, morbidity and mortality, especially in developing countries.

For which one of the following viruses is there an approved vaccine?

- A Rotavirus
- B Norovirus
- C Sapovirus
- D Enteric adenovirus
- E Astrovirus

Question 3

An outbreak of acute disease with diarrhoea and vomiting has occurred in a school. Norovirus has been diagnosed as the cause. The school is being closed and subjected to appropriate disinfection procedures. In order to judge whether children had become infected during the outbreak at school, knowledge of the incubation period is important.

What is the average duration of the incubation period for acute norovirus gastroenteritis?

- A 3–6 hours
- B 6–12 hours
- C 12–48 hours
- D 5–10 days
- E >10 days