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Viral gastroenteritis
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Abstract
This article reviews the virology, immunology and epidemiology of the most common viral causes of acute gastroenteritis (rotaviruses, human caliciviruses, astroviruses and enteric adenoviruses). The clinical symptoms span 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 mentioned. The clinically most important development in this field over the past 3 years has been the wide application of the new live attenuated rotavirus vaccines in universal mass vaccination programmes in many countries.

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

Acute gastroenteritis with vomiting are easily recognized as a clinical entity, but may be caused by very different agents (viruses, bacteria, parasites), or may 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, 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. Their appearance by electron microscopy is shown in Figure 1.

Rotaviruses
These are a major cause of infantile gastroenteritis worldwide.

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.

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, seven to eight groups/species (A–G/H) 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 types 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 of the small intestine. After virus adsorption to sialic acid, human blood group antigens and various co-receptors, viral replication takes place, first in cytoplasmic inclusions bodies termed ‘viroplasms’ followed by maturation in contact with the endoplasmic reticulum. Mature particles are released from cells by lysis. Rotavirus replication in the gut is rapid and reaches high titres (up to $10^{11}$ virus particles/ml faeces at the peak of acute diarrhoea) within a short period of time. The diarrhoea arises from epithelial necrosis and atrophy, leading to reduced absorption of carbohydrates and increased osmotic pressure in the gut lumen. There is also a component of hypersecretion which contributes to the diarrhoea. The rotavirus non-structural protein 4 (NSP4) functions as a viral enterotoxin.

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 coproantibodies of the immunoglobulin A (IgA) subclass have been identified as an important correlate of protection.

Caliciviruses
Noroviruses (previously termed ‘Norwalk-like viruses’) and sapoviruses (previously termed ‘Sapporo-like viruses’) are the two (out of five) genera of the Caliciviridae family that infect humans. The human noro- and sapoviruses are classified into five to six genogroups (I–VI), with each group containing between 1 and 19 different genotypes. Noroviruses of different genotypes co-circulate but genotype II–4 noroviruses predominate worldwide. Genetic recombination among 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, calicivirus outbreaks are common in hospital settings, old people’s homes, etc. Human infections with caliciviruses elicit virus-specific immune responses, though these do not seem to provide full protection from subsequent infections.2

Astroviruses
Astroviruses are members of the Astroviridae family and have a characteristic appearance by electron microscopy (Figure 1). 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 re-infection with heterotypic strains.6

Adenoviruses
Enteric adenoviruses of subgroup F (serotypes 40 and 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 and others decrease the expression of host cell proteins, for example, major histocompatibility complex (MHC) class I antigens on the surface of infected cells, thereby reducing susceptibility to adenovirus-specific cytotoxic T cells. A serotype-specific humoral immune response provides homotypic protection.4

Epidemiology

Rotaviruses
Infections occur endemically worldwide, causing over 450,000 deaths each year in children aged under 5 years, mainly in low-income countries of sub-Saharan Africa and South East Asia.8 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, G2, G3, G4 and G9 represent more than 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.7 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

| Virus (family) | Size and structure | Genome composition | Classification | Epidemiology |
|---------------|--------------------|--------------------|---------------|--------------|
| Rotaviruses   | 75 nm, triple-layered, wheel-shaped | 11 segments of dsRNA totalling 18.5 kb | Groups A—H | Endemic in children worldwide, winter outbreaks in temperate climates, small epidemics in the elderly |
| Caliciviruses | About 30 nm, surface cup-shaped | ssRNA, 7.7 kb | Within group A subgroups, G and P types | Epidemics in humans of all age groups |
| Enteric adenoviruses | About 70 nm, icosahedral | dsDNA, 36 kb | Genotypes of all segments | Epidemic in children |
| Astroviruses | About 30 nm, star-like appearance | ssRNA, 6.8 kb | Two genera infecting humans noroviruses sapoviruses | Epidemics in children and adults |

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Table 2
adults in China in the 1980s, and recently in Calcutta, India and in 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 (RV) vaccination (see below) noroviruses are now becoming the main cause of acute gastroenteritis in children.9 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 on 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 rotavirus or enteric adenoviruses. Infection may be accompanied by abdominal cramps, headache, myalgia and projectile vomiting, which are regarded as typical of norovirus infection. After rotavirus infection, all
degrees of severity of clinical symptoms are seen. The outcome depends on viral pathogenicity factors and on the host 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. Extra-intestinal spread of rotaviruses has been reported and may 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**

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 are replicated 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 (RT)-PCR for rotaviruses, caliciviruses and astroviruses.

**Management**

Treatment is mainly by oral rehydration 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 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 and removal of sources of infection (food, water, food-handlers), along with measures to improve environmental hygiene.

**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. Since the licensed RV vaccine contains live, attenuated viral proteins, attention is focused on the development of virus-like particles (obtained from baculovirus recombinant co-expressed RV proteins), enhancement of rotavirus immunogenicity by micro-encapsulation, DNA-based, and possibly ‘edible’ preparations as candidate vaccines.

So far, no vaccines against other viruses causing gastroenteritis in humans have been licensed. A vaccine candidate specific for norovirus genotype II-4 is under development and seems promising, as its targeted use in healthcare settings could reduce hospital-acquired infection.
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