



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.

Enteric Viruses[☆]

RF Bishop and CD Kirkwood, Murdoch Childrens Research Institute, Melbourne, Vic, Australia

© 2014 Elsevier Inc. All rights reserved.

Introduction	1
Viruses Associated With Acute Gastroenteritis	2
Caliciviruses	2
History	2
Classification	2
Geographic and Seasonal Distribution of Human Norovirus	3
Genetics	3
Pathogenesis	3
Immune Responses, Prevention and Control	4
Rotaviruses	4
History	4
Classification	4
Geographic and Seasonal Distribution	4
Host Range	5
Genetics	5
Pathogenesis	5
Clinical Features	5
Immune Response/Prevention and Control	6
Adenovirus	6
History and classification	6
Geographic and Seasonal Distribution	7
Genetics/Evolution	7
Pathogenesis	7
Clinical Features	7
Astroviruses	7
History and Classification	7
Genetics and Evolution	7
Pathogenesis	8
Coronaviruses/Toroviruses	8
Picornaviruses	9
Parvoviruses	9
Picobirnaviruses	9

Introduction

The intestinal tract, lined by replicating epithelial cells bathed in nutrient fluids and maintained at optimal temperature provides an ideal milieu for growth of many viruses. 'Enteric viruses' represent a wide spectrum of viral genera that invade and replicate in the mucosa of the intestinal tract, and that can be grouped as follows:

- Viruses causing localised inflammation at any level of the intestinal tract, predominantly in small intestinal mucosa, resulting in acute gastroenteritis for example rotaviruses, caliciviruses, adenoviruses, astroviruses, coronaviruses.
- Viruses that multiply at any level of the intestinal tract, causing few enteric symptoms prior to producing clinical disease at a distant site for example measles virus, Reoviruses (in mice), Enteroviruses (including polioviruses, coxsackieviruses, enteroviruses, Hepatitis A and E).
- Viruses that spread to the intestinal tract during the later stages of systemic disease, generally in an immunocompromised host for example HIV virus, cytomegalovirus.

This article will focus upon the first category of viruses that cause enteric disease associated with primary replication in the intestinal tract.

[☆]*Change History:* July 2014. RF Bishop and CD Kirkwood updated the sections Pathogenesis and Immune response, prevention and control under the heading Caliciviruses and has updated Classification and Immune response, prevention and control under the heading Rotaviruses. And have added new articles to the Further reading section.

Viruses Associated With Acute Gastroenteritis

Acute gastroenteritis is one of the most common health problems worldwide. More than 700 million cases are estimated to occur annually in children less than 5 years of age, resulting in few deaths in developed countries, but more than 2 million deaths in developing countries.

Worldwide, a diverse group of viral, bacterial and parasitic pathogens, cause acute enteric symptoms including nausea, vomiting, abdominal pain, fever and acute diarrhoea. Infections with viral agents, unlike those with bacterial or parasitic pathogens, cannot be treated with antibiotics, and many cannot be prevented by improvements in quality of drinking water, food or sanitation.

Until the early 1970s most viral agents causing gastroenteritis in humans were largely unknown. Studies using electron microscopy of intestinal contents resulted in the discovery of numerous viral enteropathogens now classified as caliciviruses, rotaviruses, astroviruses or 'enteric' adenoviruses. Caliciviruses are now recognised as the most important cause worldwide of outbreaks of viral gastroenteritis in humans of all age groups. Rotaviruses are the single most important cause of life-threatening diarrhoea in children <5 years old. Astroviruses and adenoviruses also cause severe diarrhea in children (Table 1). Other viruses linked to gastroenteritis in humans include coronaviruses, torovirus, picornaviruses and picobirnaviruses. Understanding many features of these 'enteric viruses' has been based on parallel studies of related viruses infecting animals.

Caliciviruses

History

The family *Caliciviridae* contain small RNA viruses that cause enteric disease in a wide variety of hosts including cattle, pigs, rabbits and humans. Infections in other hosts, for example sea lions, cats and primates appear to cause predominantly systemic and respiratory symptoms. Caliciviruses are small non-enveloped viruses of 27–34 nm diameter (Figure 1) with a genome comprising a single stranded positive sense polyadenylated RNA genome of 7400–7700 nucleotides. Typical calicivirus particles show cup-like hollows (calices) on the virus surface. Some caliciviruses have an indistinct appearance described as 'feathery'.

The 'Norwalk agent' (now classified as a calicivirus) was identified in 1972 by Kapikian and colleagues, using immune electron microscopy (IEM) to search for the causative agent of an 1968 outbreak of gastroenteritis in humans in Norwalk, Ohio, USA. Many related viruses have been implicated as causes of gastroenteritis, and given names identifying the geographical location of the outbreak (eg. Marin County, Snow Mountain, Hawaii, Sapporo).

Classification

Classification of caliciviruses was hampered for many years by the inability to culture these viruses, and study their genetic and protein structure. Caliciviruses causing enteric infections (in humans and other animals) are classified as belonging to the family *Caliciviridae*, which is divided into four genera. The genus *Norovirus* (NoV), and genus *Sapovirus* (SaV) cause human and animal infections. Other genera infect rabbits (*Lagovirus*) or sealions, cats and primates (*Vesivirus*). The genome organization and reading frame usage differs between the four genera. For noroviruses, the genome contains 3 open reading frames (ORFs). The largest

Table 1 Characteristics of major enteric viruses causing acute gastroenteritis in humans

Characteristic	<i>Norovirus/Sapovirus</i>	<i>Rotavirus</i>	<i>Adenovirus</i>	<i>Astrovirus</i>
Family	Caliciviridae <i>Divided into genogroups, each with distinct genetic clusters</i>	Reoviridae <i>6 groups (A-F)</i> Group A- multiple serotypes based on outer capsid proteins.	Adenoviridae <i>6 subgenera, more than 50 serotypes.</i> <i>Enteric serotypes (Ad40-41)</i>	Astroviridae <i>8 serotypes</i>
Virion size (nm)	28-35	70	80	28
Capsid organisation	Two structural proteins (orf2-56-62kd, orf3-22kd)	Two outer capsid proteins (VP7-38kd, VP4-88kd) Two inner protein layers (VP6- 41kd, VP2-88kd)	Capsomer- composed of three proteins; Hexon-, penton-, and fibre-	Precursor cleaved into several proteins (eg 20kd, 29kd & 31kd)
Nucleic acid	ss RNA (plus sense)	ds RNA	dsDNA	ss RNA (plus sense)
Genome organisation	3 open reading frames (1, 2 & 3).	11 segments which encode specific protein.	Linear chromosome with multiple transcription/translation units	2 open reading frames (1a, 1b & 2)

ss = single stranded.
ds = double stranded.
kd = kilodalton.

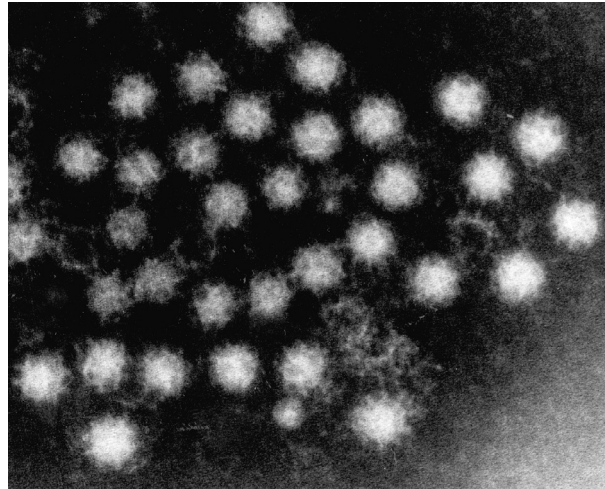


Figure 1 Electron micrograph of negatively-stained calicivirus particles (NoV) in faecal extract.

(ORF1) encodes a polyprotein which undergoes proteolytic cleavage to produce an NTPase, a 3c-like protease and an RNA dependent RNA polymerase (RdRp). ORF 2 encodes the major capsid protein and ORF3 encodes a putative minor capsid protein.

Noroviruses are subdivided into five genogroups (GI to GV). Genogroup GI, GII and GIV infect humans, GIII infect cattle and GV infect mice. GI and GII contain at least 10 and 20 distinct genetic clusters respectively. Sapoviruses are divided into genogroups (GI to GV), of which GI, GII, GIV and GV infect humans. GI and GII are further divided into 4 and 3 genetic clusters.

The inability to culture human caliciviruses delayed the introduction of diagnostic tests, resulting in an under-appreciation of the significance of these agents for many years. Currently over 20 different RT-PCR assays targeting regions on the RdRp gene and the capsid gene have been described and utilised in epidemiological studies. *This* large genetic diversity of human caliciviruses makes routine detection difficult.

Geographic and Seasonal Distribution of Human Norovirus

Human noroviruses (NoV) are the leading causes of 'non-bacterial gastroenteritis' outbreaks in all age groups worldwide. Outbreaks frequently occur in communities such as nursing homes, hospitals, schools, and cruise ships. No consistent seasonal variation has been observed. Infection involves transmission via person-to-person contact or ingestion of contaminated food and water.

Epidemiological studies have identified noroviruses in 60-95% of outbreaks in many countries. Estimates of disease burden in USA suggest that caliciviruses are responsible annually for 20 million illnesses and 70 000 hospitalisations. Although human NoV are a genetically diverse group of viruses, strains of NoV GII cluster 4 (GII.4) have been the most common type identified worldwide associated with 70-80% of all outbreaks in both adults and children. Prevalence rates of calicivirus (predominantly NoV) in young children admitted to hospital with acute gastroenteritis in many countries, range from 3.5%-20% annually. Strains of SaV, while playing a minor role overall, are more generally associated with childhood gastroenteritis than with disease in older children and adults. Caliciviruses may be important enteric pathogens in patients with hereditary or acquired immunodeficiency.

Genetics

The *Norovirus* and *Sapovirus* genera are genetically diverse, and multiple strains co-circulate in human populations. Individual dominant strains emerge every 2-5 years, and often have a global impact. From the 1990s to 2013 GII.4 strains are the most commonly identified strain responsible for large global outbreaks, identified in multiple outbreak settings in USA, Europe, Japan and Australia in 1995/1996, 2004, 2007 and again in 2011.

NoV recombinant strains, with polymerase and capsid genes derived from different ancestral clusters, have been identified in Thailand and Australia. Repeated attempts to adapt NoV and SaV to growth in cell culture have failed. Diagnostic techniques, and analysis of antigenic variation rely predominantly on molecular biological techniques. Cloning and expression of the major viral capsid protein (VP1) in baculovirus expression systems has led to the formation of virus-like particles (VLP) morphologically similar to native virus and their incorporation into EIA assays.

Pathogenesis

Pathogenesis of human NoV and SaV infection is poorly understood as a result of the long-standing inability to adapt these human viruses to cell culture. In recent years, however, the development of murine and porcine models has begun to improve our understanding of norovirus pathogenesis.

The precise tropism of human norovirus is unknown. However, symptomatic enteritis in human volunteers infected with 'Norwalk agent' showed changes in jejunal biopsies (mucosal inflammation, absorptive cell abnormalities, villus shortening and crypt hypertrophy) that persisted for at least 4 days after remission of clinical symptoms and reverted to normal after 2 weeks. No identifiable viral particles were detected by electron microscopy in any affected intestinal tissue. The recent demonstration that human noroviruses can infect and replicate in a 3-dimensional cell culture model of human intestinal epithelium, should improve our understanding of the pathogenesis, and antigenic diversity of this important group of enteric viruses.

The process of norovirus attachment to host cells and internalization is not well known, however, substantial work has shown that human noroviruses recognise histo-blood group antigens (eg. ABO, H and Lewis group antigens) expressed on gastrointestinal tissues.

Immune Responses, Prevention and Control

Mechanisms of immunity to NoV are unclear. Infection results in formation of IgG and IgM serum antibody that are broadly reactive within, but not between, genogroups. The role of these antibodies in immune protection is unknown. Infected individuals can develop short-term immunity to homologous viruses but the molecular diversity of NoV circulating in communities makes it difficult to predict whether long-term immunity can develop. It is unclear why a proportion of exposed individuals remain uninfected during outbreaks. Recent studies suggest that histo-blood group antigens and the secretor status may be genetic susceptibility markers for infection.

Current NoV vaccine development relies on production and evaluation of virus-like particles and other subviral particles as capsid subunit vaccines. Human trials for virus-like particle (VLP)-based vaccines show promise in both immune response and protection studies, with availability of vaccines being targeted over the next 5 years. Control strategies for prevention of human infection also continues to rely on prevention of contamination of food and water supplies.

Rotaviruses

History

Virus particles, later classified in the genus *Rotavirus*, were first described in 1963 by Adams and Kraft as a cause of epidemic diarrhoea in infant mice (EDIM). Similar particles (NCDV) were recognised in 1969 by Mebus and colleagues as a cause of severe diarrhoea in newborn calves in Nebraska, USA. Neither virus was considered relevant as a causative agent of severe diarrhoea in young children until 1973 when Bishop, Davidson, Holmes and Ruck described a 'new virus' (later shown to be antigenically related to EDIM and NCDV) in duodenal biopsies and diarrheal faeces from young children admitted to hospital in Melbourne, Australia with severe acute diarrhoea. Named because of their wheel-like appearance in negatively stained extracts examined by electron microscopy (rota = Latin for wheel) rotaviruses have since become established as causes of severe acute diarrhoea in the young of many mammalian and avian species worldwide. Rotavirus enteritis affects all children regardless of socio-economic status, and results in over 500 000 deaths annually in young children in developing countries.

Classification

Rotaviruses are non-enveloped icosahedral viruses of 70 nm (Figure 2) diameter that belong to the genus *Rotavirus* within the family *Reoviridae*. The double stranded RNA genome is contained within a triple-layer of viral proteins (VP) comprising a core (VP1, VP2, VP3), an inner capsid (VP6) and an outer capsid (VP4, VP7). Rotaviruses are classified into Groups A to G based on serology of the VP6 protein, with the majority of human and mammalian infections, due to Group A viruses. Groups B and C have been identified infrequently in humans. Groups D to G have been identified only in non-human mammalian or avian species.

A binary classification system based on the genetic sequence of the genes encoding the two outer capsid proteins VP7 and VP4 is used to type viruses into G and P genotypes. To date there are at least 37 G-genotypes and 35 P-genotypes identified in humans and animals. A system to classify the whole genome constellation has been recently developed based on nucleotide sequence of the open reading frame for each gene; VP7, VP4, VP6, VP1, VP2, VP3, NSP1, NSP2, NSP3, NSP4, and NSP5/NSP6 is Gx-P[x]-Ix-Rx-Cx-Mx-Ax-Nx-Tx-Ex-Hx.

Geographic and Seasonal Distribution

Five rotavirus genotypes G1P[8], G3P[8], G4P[8], G2P[4] and G9P[8] have been the most common types causing severe human disease globally during the past 30 years. G1P[8] strains have been consistently present worldwide. Yearly winter epidemics of rotavirus disease are regularly observed in countries with temperate climates, whereas rotavirus disease is prevalent year round in tropical climates lacking defined winter seasons.

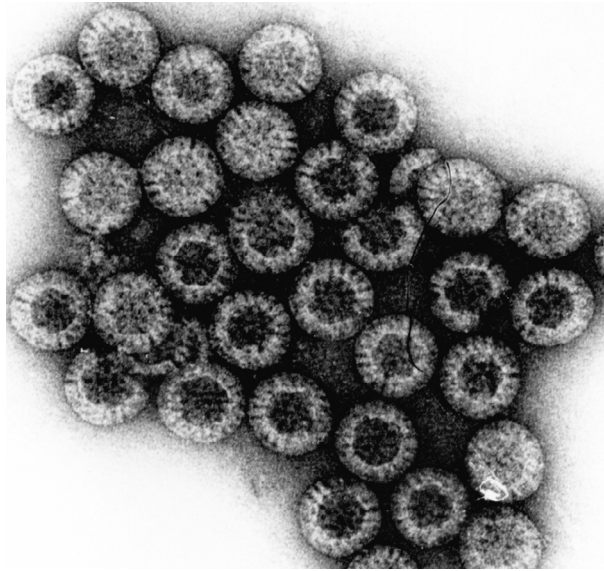


Figure 2 Electron micrograph of negatively-stained triple-shelled rotavirus particles in faecal extract.

Host Range

Group A rotaviruses infect humans and other mammals repeatedly throughout life. Most primary rotavirus infections in animals occur during the neonatal period. Most primary rotavirus infections in humans occur during the first 24 months of life. Children worldwide will experience at least one rotavirus infection by 5 years of age.

In general, Group A rotaviruses are species specific. However rotavirus strains with gene segments of feline, bovine, or porcine origin have been isolated from children, suggesting the occurrence of cross-species infection in nature. Cross species infections can be established experimentally, and comprise one of the strategies for human vaccine development.

Genetics

The rotavirus genome consists of 11 segments of double stranded RNA that can be separated by polyacrylamide gel electrophoresis, allowing epidemiological studies mapping the genetic diversity of strains within and between serotypes. Each gene segment encodes a separate protein, with the exception of gene segment 11 which encodes 2 proteins. Reassortment of genes between human strains and human and animal strains occurs *in vivo* and *in vitro*.

Pathogenesis

Rotaviruses are transmitted from person to person by the faecal oral route, or via aerosols. Rotaviruses replicate in the cytoplasm of mature non-replicating enterocytes lining the upper portions of the small intestinal villi, eventually causing cytolysis. Profuse watery diarrhoea results from a combination of mechanisms including malabsorption secondary to loss of enterocytes responsible for absorption and digestion, activation of the enteric nervous system and stimulation of intestinal secretion by the rotavirus non-structural protein NSP4. Rotavirus antigenemia and viremia occur during the acute phase of severe primary rotavirus disease. As a result, complete rotavirus particles have been found in liver, lung, spleen, pancreas, thymus and kidneys of experimental animals. It is not clear if the virus is replicating at these sites.

Clinical Features

Clinical symptoms in children are strongly influenced by age, with severe often life-threatening diarrhoea occurring after primary infection in young children, and in aged people in nursing homes. Excretion of rotavirus particles in detectable numbers (by EIA, RT/PCR) continues for 5–10 days, and occasionally up to 50 days. Excretion can continue for months in immunodeficient children and animals. Reinfections occur throughout life, and are usually asymptomatic or associated with mild symptoms. Symptoms of primary infection require medical attention in 1:5 children, result in hospitalisation in 1:65 children and death in 1:293 (almost all in young children in developing countries). Treatment is based upon replacement of fluid and electrolyte loss, usually achieved by oral administration of fluids containing glucose and electrolytes. Occasionally, delayed repair of the small intestinal mucosa is associated with disaccharide or monosaccharide malabsorption leading to malnutrition.

Immune Response/Prevention and Control

Primary rotavirus infection protects against severe symptomatic disease on reinfection, and is associated with humoral and cellular immune responses to individual rotavirus proteins. Neutralising antibody to VP4 and VP7 outer capsid proteins contribute to protection, possibly by interfering with viral replication and limiting the extent of intestinal damage. The role of immune responses to other proteins is uncertain. Virus-specific cytotoxic T cells are not essential for protection. The development of a rotavirus vaccine has been a priority to reduce the global burden of disease caused by rotavirus infection. The basis for vaccine development was the observation of immune protection arising from natural infection. Primary natural infections generally produce homotypic protection (single genotype) and subsequent infections result in a heterotypic immune response (multiple genotypes).

The importance of rotavirus disease worldwide and its contribution to childhood mortality in developing countries has resulted in strong initiatives, supported by the World Health Organisation, including the recent recommendation in 2009 of introduction of rotavirus vaccination into all routine immunization programs for infants globally.

The first available rotavirus vaccine; Rotashield (Wyeth Lederle Vaccines, USA) was licensed in USA in 1998 for use in infants as an oral, tetravalent, rhesus-human reassortant strain vaccine administered in a three dose schedule. It was withdrawn from the global market in late 1999 due an association with rare event, intussusception; a telescoping of the bowel which can be fatal without medical intervention.

Two live-oral vaccines (Rotarix and RotaTeq) were subsequently developed and shown to be safe and highly effective at preventing severe and moderate rotavirus disease in large Phase III clinical studies in many settings across the globe. RotaTeq (Merck & Co., USA) is a live-attenuated pentavalent vaccine that contains five genetically distinct human-bovine reassortant virus strains (Vesikari, 2006). Each reassortant strain contains a human gene, encoding one of the outer capsid proteins (G1, G2, G3, G4 and P[8]), within a bovine strain backbone (G6P[5]). RotaTeq is administered orally as a three dose schedule, recommended at two, four and six months of age. Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) is a monovalent vaccine containing a single strain (RIX4414) of the most prevalent genotype worldwide (G1P[8]) and is administered orally at two and four months of age. Several other vaccine candidates are in various stages of development and licensure including neonatal strains isolated in India and Australia and bovine-human reassortant vaccine strains.

The inclusion of rotavirus vaccines into the routine vaccination programs of numerous countries has resulted in a significant reduction in rotavirus associated deaths, hospitalisations, emergency room visits and episodes of gastroenteritis. Highlighting the benefit and real world effectiveness of rotavirus vaccines.

Adenovirus

History and classification

Adenoviruses were first detected in 1953 in cultured fragments of tonsillar and adenoidal tissue from children. They are non-enveloped icosahedral viruses approximately 80 nm in diameter (Figure 3). The genome is composed of double-stranded DNA. The Family *Adenoviridae* comprises *three* Genera: *Mastadenovirus* (mammalian) classified into sub-Genera A to F representing more than 50 serotypes, *Aviadenovirus* (birds), and a newly recognised Genus *Atadenovirus* identified in sheep and reptiles. Most are readily cultivatable. Adenovirus infections occur worldwide in many mammalian species, are species specific, usually associated

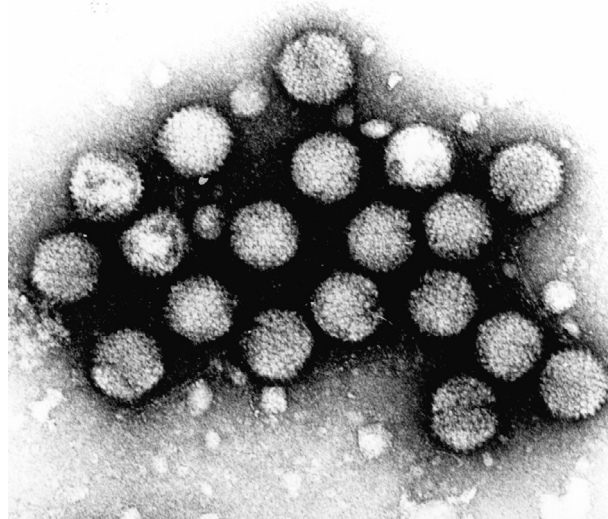


Figure 3 Electron micrograph of negatively-stained 'enteric' adenovirus particles (showing characteristic hexagonal shape) in faecal extract.

with disease in the respiratory, urinary and ocular systems, and are frequently shed in faeces in the absence of any gastrointestinal symptoms.

In 1975, Flewett and colleagues in Birmingham, UK, noticed the presence of large numbers of adenovirus particles in negatively stained extracts of diarrheal stools examined by EM. These proved difficult to culture, were designated 'enteric' adenoviruses (EAd), and are now classified as serotypes EAd40 and EAd41 within sub-Genus Group F. Cultivation of EAd remains difficult. The most reliable growth has been achieved in human embryonic kidney cells (293 cells) immortalised by transfection with regions of Ad5.

Geographic and Seasonal Distribution

EAd40 and EAd41 occur worldwide, causing severe acute enteritis in 5-15% of hospitalised young children. Outbreaks occur at unpredictable intervals year round with no seasonal prevalence. Nosocomial epidemics occur in day-care nurseries and in hospital wards for children and adults. Group A adenoviruses (serotypes 12, 18, 31) have also been implicated in epidemics, usually in older age groups.

Genetics/Evolution

The adenovirus virion is composed of at least 10 different structural polypeptides and contains a linear 33–45 kilobase-paired DNA. Virus capsomers are arranged as hexons, the corners of which have antenna-like (fibre) projections presumed involved in cell attachment. The DNA genomes of Groups A to F are genetically diverse, and differences can be illustrated by analysis using genome restriction endonucleases. The heterogeneous genome in Groups A to F makes recombination between subgenera unlikely, with exception of Groups A and F which show a close evolutionary relationship.

Diagnoses of EAd infection relies on EIA that detects the hexon antigen common to Groups A to F, followed by determination of restriction enzyme patterns and/or reactions in EIA incorporating neutralising, monoclonal antibodies specific for Ed40 and 41.

Pathogenesis

EAd replicate within the epithelial cells of the small intestine. Group A adenoviruses have also been grown from mesenteric lymph nodes and appendices. The mechanisms causing diarrhoea are not clear, but destruction of infected epithelial cells has a role.

Clinical Features

Adenovirus diarrhoea is more common in infants <12 months old than in older children, and can be protracted with a mean duration of 12 days. Adenovirus diarrhoea occurs in immunocompromised patients. Non-seasonal epidemics of EAd diarrhoea occur in hospital wards, orphanages, and day-care nurseries. Occasional fatal cases have been reported in children. Evidence from animal models (with non-EAd) suggests that viraemia occurs, and can lead to infection of other tissues. The natural history of disease and development of immunity is unknown.

Astroviruses

History and Classification

Astroviruses were first described in the UK in 1975 by Madeley and Cosgrove studying an outbreak of diarrhoea in newborn babies in an obstetric hospital nursery. Astroviruses are small, round non-enveloped plus-stranded RNA viruses 28–30 nm diameter (Figure 4) occasionally exhibiting virions with a superficial star shape. They are members of the genus *Astrovirus* in the Family *Astroviridae*. They have been detected in humans (children and adults) and a range of mammalian (sheep, cattle, pigs, dogs, cats and mice) and avian (turkeys, ducks) species, usually associated with diarrhoea. There are currently eight serotypes of human astrovirus, designated HAstV 1 to 8, based on reactivity with polyclonal antisera. HAstV 1 is most common worldwide.

Prevalence rates as a cause of diarrhoea vary from 2-16% (hospital-based studies), and 5-17% (community-based studies). Most astrovirus infections have been recorded during colder months in temperate climates and year-round in tropical countries. A longitudinal study in Mayan children in a poor community in Mexico found a high prevalence (61%) of astrovirus infection in a birth cohort of 271 children followed for 3 years. Infection occurred primarily in infants <12 months old, and showed a high rate of asymptomatic infection and prolonged shedding (2–17 weeks) in many infants. Astrovirus infection has also been associated with persistent diarrhoea (lasting for 14 days or more) in children in Bangladesh. Astroviruses are widespread in developed countries, causing outbreaks in day care centres, hospitals, and nursing homes for the elderly. They are an important cause of enteritis in immunocompromised patients.

Genetics and Evolution

The HAst genome is a polyadenylated plus-strand RNA molecule of approximately 7 kilobases. The genome contains 2 open reading frames (ORF), ORF 1a and 1b, code for non-structural proteins and ORF 2 encodes for the capsid protein. Genetic diversity

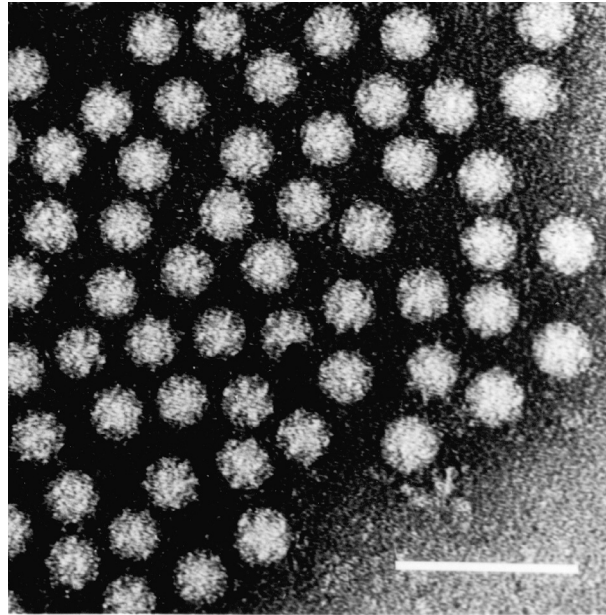


Figure 4 Electron micrograph of negatively-stained astrovirus particles (showing star-shape) in faecal extract.

in all serotypes exists, but no association has been shown between serotypes and ability to cause severe gastroenteritis. Astrovirus diagnostic assays include commercially available EIA kits, electron microscopy and RT-PCR detection and genotyping of diarrhoeal faeces.

Pathogenesis

Acute astrovirus infection induces a mild watery diarrhoea in young children that lasts for 2–3 days and may be associated with vomiting, fever and anorexia. The lack of a small animal model has hampered studies of the mechanism of astrovirus-induced diarrhoea. Experimental models of astrovirus enteritis in turkeys and in gnotobiotic lambs show mild histopathological changes in the intestine (despite high mortality from severe osmotic diarrhoea) together with viraemia. Experimental astrovirus infection in calves is asymptomatic, with viral replication apparently targeted to M cells. It is possible that none of these animal models illuminate pathogenesis of HAsV infection in humans. Cultivation of HAsV was initially difficult, but can now regularly be achieved using a human colon cancer derived epithelial cell line (CaCo2 cells).

Coronaviruses/Toroviruses

Members of the genera *Coronavirus* and *Torovirus* are enveloped plus strand single-stranded RNA viruses belonging to the Family *Coronaviridae*. Electron microscopy shows them to be pleomorphic fringed particles 100–140 nm at maximum dimension (Figure 5). Coronaviruses and toroviruses can be distinguished by differences in peplomer structure and reaction in IEM using specific antisera.

Coronaviruses and Toroviruses cause diarrhoea, respiratory and/or hepatic disease in many animal species including cattle, mice, swine, cats and dogs. In general, most of these viruses are species-specific and disease is most severe in infant animals. Transmission is faecal-oral and due to virus lability may require close contact. Coronaviruses and Torovirus have been implicated in human diarrhoeal disease but there is still no consensus about their importance. Similar particles have been seen frequently in children without diarrhoea, particularly in children in developing countries. Morphological similarities between these viruses and fragments of intestinal brush border make diagnosis difficult. Several studies have implicated Coronaviruses as causative agents of necrotizing enterocolitis outbreaks in newborn babies.

Toroviruses were first described as a cause of diarrhea by Woode and colleagues in 1979 when Breda virus was identified in a severe outbreak of neonatal calf diarrhoea in USA. Toroviruses are now also known to infect horses (Berne virus) and swine. Human infections were first described by Flewett et al. in Birmingham UK in 1984, but have rarely been reported since then.

The pathogenesis of diarrhoea has been studied in animal models using infection with coronavirus (TGE) in piglets, and with Breda viruses in calves. Both replicate in epithelial cells of small intestine and descending colon causing diarrhoea 24–72 h later. Breda virus also replicates in crypt cells.

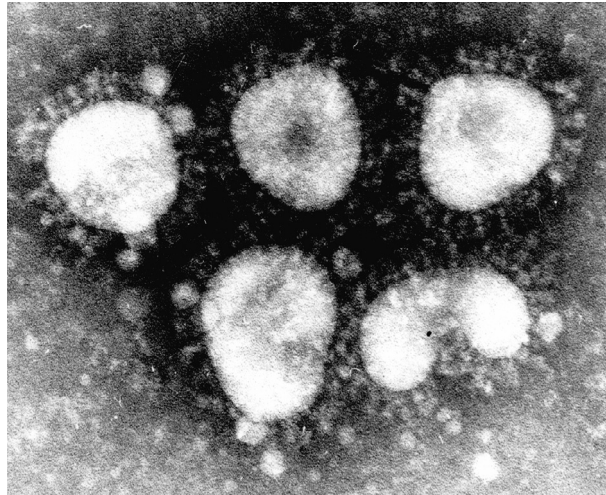


Figure 5 Electron micrograph showing large fringed pleomorphic coronavirus particles (with adherent antibody) in faecal extract.

Many animal coronaviruses can be propagated in cell culture. Isolation of human enteric coronaviruses is difficult and serological studies can be confounded by antibody resulting from repeated respiratory coronavirus infection. Enteric infection can be confirmed in feces by detection of viral RNA by RT-PCR, or IEM using antibodies to the viral envelope glycoproteins.

Picornaviruses

Picornaviruses are 24–30 nm featureless spherical particles containing single stranded positive sense RNA. That have been found in diarrheal feces from humans but their etiological role is often not clear. The first clear evidence implicating a picornavirus as an enteric pathogen identified Aichi virus, as a cause of oyster-associated epidemics of gastroenteritis in Japan in 1989. Aichi viruses are now classified as a new Genus Kobuvirus within the family Picornaviridae (kobu = Japanese for knob). Isolation of Aichi virus in Vero cells has permitted development of EIA and RT-PCR assays based on nucleotide sequence data. Serological assays show seroconversion resulting from infection and a prevalence rate for antibody of 7.2% in Japanese children aged 7 months to 4 years and rising to 80% in adults by age 35.

The new Genus *Parechovirus* within the Family *Picornaviridae* contains at least one serotype (previously echovirus 22) that has been implicated as an enteric pathogen in humans.

Parvoviruses

Parvoviruses are small 22–26 nm single stranded DNA viruses comprising a Genus Parvovirus in the Family *Parvoviridae*. Some animal parvoviruses have been clearly linked to enteritis including bovine, feline, mink and canine strains. Canine parvovirus infection emerged after 1977. This lethal neonatal enteric infection, accompanied by viraemia and widespread systemic infection shows a pathogenesis distinct from most enteropathogenic viruses. The virus infects and destroys crypt epithelial cells resulting in flat mucosa with fused and stunted villi. Damage has been likened to that caused by radiation.

Other small viruses, resembling parvoviruses have been seen by EM in diarrheal faeces in humans. Evidence linking them to causation of disease is not convincing. They have often been present as dual infections with known enteric pathogens. In addition, their resemblance to some phages makes diagnosis uncertain.

Picobirnaviruses

These are a group of currently unclassified small viruses detected in the faeces of humans and animals without diarrhea. Picobirnaviruses are 35–41 nm particles with a bi- or tri- segmented dsRNA genome and have been detected in Europe, South America and Australia. They are found significantly more often in patients with HIV-related diarrhoea than those without diarrhoea. The role in gastroenteritis in healthy individuals remains unknown.

Further Reading

- Atmar RL and Estes MK (2001) Diagnosis of noncultivable gastroenteritis viruses, the human caliciviruses. *Clinical Microbiology Reviews* 14: 15–37.
- Bressee JS, Widdowson M-A, Monroe SS, and Glass RI (2002) Foodborne viral gastroenteritis: challenges and opportunities. *Clinical Infectious Diseases* 35: 748–753.
- Chadwick D and Goode JA (2001) Gastroenteritis Viruses. In: Novartis Foundation Symposium 238, New York: John Wiley & Sons.
- Viral gastroenteritis. Chiba S, Estes MK, Nakata S, and Calisher CH (eds.) (1996) *Archives of Virology* (Supplement 12): 119–128.
- Dennehy PH (2012) Effects of vaccine on rotavirus disease in the pediatric population. *Current Opinion in Pediatrics* 24: 76–84.
- Duckmanton L, Luan B, Devenish J, Tellier R, and Petric M (1997) Characterisation of torovirus from human faecal specimens. *Virology* 239: 158–168.
- Franco MA, Angel J, and Greenberg HB (2006) Immunity and correlates of protection for rotavirus vaccines. *Vaccine* 24: 2718–2731.
- Glass RI (2006) New hope for defeating rotavirus. *Scientific American* 294: 33–39.
- Hall GA (1987) Comparative pathology of infection by novel diarrhoea viruses. In: Bock G and Whelan J (eds.) Novel diarrhoea viruses. Ciba Foundation Symposium 128, pp. 192–217. Chichester: John Wiley & Sons.
- Hall AJ, Lopman BA, Payne DC, Patel MM, Gastañaduy PA, Vinjé J, and Parashar UD (2013) Norovirus disease in the United States. *Emerging Infectious Diseases* 19: 1198–1205.
- Hansman GS, Oka T, Katayami K, and Takeda N (2007) Human Sapovirus: genetic diversity, recombination and classification. *Reviews in Medical Virology* 17: 133–141.
- Karst SM (2010) Pathogenesis of noroviruses, emerging RNA viruses. *Viruses* 2: 748–781.
- Matthijnssens J, Ciarlet M, McDonald SM, Attoui H, Banyai K, Brister JR, Buesa J, Esona MD, Estes MK, Gentsch JR, Iturriza-Gomara M, Johne R, Kirkwood CD, Martella V, Mertens PP, Nakagomi O, Parreno V, Rahman M, Ruggeri FM, Saif LJ, Santos N, Steyer A, Taniguchi K, Patton JT, Desselberger U, and Van Ranst M (2011) Uniformity of rotavirus strain nomenclature proposed by the Rotavirus Classification Working Group (RCWG). *Archives of Virology* 156: 1397–1413.
- Mendez-Toss M, Griffin DD, Calva J, et al. (2004) Prevalence and genetic diversity of human astroviruses in Mexican children with symptomatic and asymptomatic infections. *Journal of Clinical Microbiology* 42: 151–157.
- Ramig RF (1997) Genetics of the rotaviruses. *Annual Review of Microbiology* 51: 225–255.
- Ramig RF (2004) Pathogenesis of intestinal and systemic rotavirus infection. *Journal of Virology* 78: 10213–10220.
- Schwab KJ, Estes MK, and Atmar RL (2000) Norwalk and other human caliciviruses: molecular characterization, epidemiology and pathogenesis. In: Cary JW, Linz JE, and Bhatnagar D (eds.) *Microbial foodborne diseases: mechanisms of pathogenesis and toxin synthesis*, pp. 469–493. Lancaster, USA: Technomic Publishing Company.
- Straub TM, Honer zu Bentrup K, Orosz-Coghlan P, et al. (2007) *In vitro* cell culture infectivity assay for human Noroviruses. *Emerging Infectious Diseases* 13: 396–403.
- Tiemessen CT and Kidd AH (1995) The subgroup F adenoviruses. *Journal of General Virology* 76: 481–497.
- Yamashita T, Sugiyama M, Tsuzuki H, et al. (2000) Application of a reverse transcription – PCR for identification and differentiation of Aichi virus, a new member of the picornavirus family associated with gastroenteritis in humans. *Journal of Clinical Microbiology* 38: 2955–2961.