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.

See also: Alphacryptovirus and *Betacryptovirus*; Hypoviruses; Totiviruses.

Further Reading

Brown GG and Finnegan PM (1989) RNA plasmids. *International Review of Cytology* 117: 1–56.

Fukuhara T (1999) Double-stranded RNA in rice. *Journal of Plant Research* 112: 131–138.

Gibbs MJ, Pfeiffer P, and Fukuhara T (2004) Genus *Endornavirus*. In: Fauquet CM, Mayo MA, Maniloff J, Desselberger U, and Ball LA (eds.) *Virus Taxonomy: Eighth Report of the International Committee on Taxonomy of Viruses*, pp. 603–605. San Diego, CA: Elsevier Academic Press.

Tavantzis SM (ed.) (2001) *dsRNA Genetic Elements: Concepts and Applications in Agriculture, Forestry, and Medicine.* Boca Raton, FL: CRC Press.

Enteric Viruses

R F Bishop and C D Kirkwood, Murdoch Childrens Research Institute Royal Children's Hospital, Melbourne, VIC, Australia

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 localized inflammation at any level of the intestinal tract, predominantly in small intestinal mucosa, resulting in acute gastroenteritis, for example, rotaviruses, caliciviruses, adenoviruses, astroviruses;
- 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); and
- viruses that spread to the intestinal tract during the later stages of systemic disease, generally in an immunocompromised host, for example, human immunodeficiency virus (HIV), cytomegalovirus.

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

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 diarrhea. 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 recognized 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 diarrhea in children <5 years old. Astroviruses and adenoviruses also cause severe diarrhea in children. **Table 1** lists the characteristics of the major viruses associated with acute gastroenteritis. Other viruses linked to gastroenteritis in humans include coronaviruses, toroviruses, 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 nonenveloped viruses of 27–35 nm diameter (**Figure 1**) with a genome comprising

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

Characteristic Family	*Norovirus/ Sapovirus Caliciviridae*	*Rotavirus Reoviridae*	*Adenovirus Adenoviridae*	*Astrovirus Astroviridae*
	Divided into genogroups, each with distinct genetic clusters	Six groups (A–F) Group A-multiple serotypes based on outer capsid proteins.	Six subgenera, more than 50 serotypes Enteric serotypes (Ad40–41)	Eight serotypes
Virion size (nm)	28–35	70	80	28
Capsid organization	Two structural proteins (orf2–56–62 kDa, orf3–22 kDa)	Two outer capsid proteins (VP7–38 kDa, VP4–88 kDa) Two inner protein layers (VP6–41 kDa, VP2–88 kDa)	Capsomer – composed of three proteins: hexon, penton, and fiber.	Precursor cleaved into several proteins (e.g., 20 kDa, 29 kDa and 31 kDa)
Nucleic acid	ssRNA (plus sense)	dsRNA	dsDNA	ssRNA (plus sense)
Genome organization	Three open reading frames (1, 2, and 3)	11 segments which encode specific protein.	Linear chromosome with multiple transcription/ translation units	2 open reading frames (1a, 1b, and 2)

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

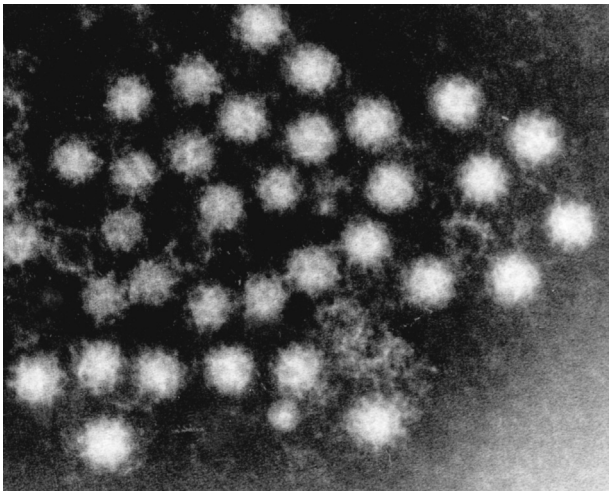

Figure 1 Electron micrograph of negatively stained calicivirus particles (NoV) in fecal extract.

a single-stranded positive-sense polyadenylated RNA genome of 7400–7700 nucleotides (nt). 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 (e.g., 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 three open reading frames (ORFs). The largest (ORF1) encodes a polyprotein which undergoes proteolytic cleavage to produce an NTPase, a 3c-like protease, and an RNA-dependent RNA polymerase (RdRp). ORF2 encodes the major capsid protein and ORF3 a putative minor capsid protein.

Noroviruses are subdivided into five genogroups (GI–GV). Genogroups GI, GII, and GIV infect humans, GIII infects cattle and GV infects mice. GI and GII contain at least 10 and 20 distinct genetic clusters, respectively. Sapoviruses are divided into genogroups (GI–GV), of which GI, GII, GIV, and GV infect humans. GI and GII are further divided into four and three 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 reverse transcription-polymerase chain reaction (RT-PCR) assays targeting regions on the RdRp gene and the capsid gene have been described and utilized in epidemiological studies. This large genetic diversity of human caliciviruses makes routine detection difficult.

Geographic and Seasonal Distribution

Human NoV are the leading causes of 'nonbacterial 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 caliciviruses in 60–95% of outbreaks in many countries. Estimates of disease burden in USA suggest that caliciviruses are responsible annually for 23 million illnesses and 50 000 hospitalizations. Strains of NoV GII cluster 4 (GII-4) have been the most common type identified worldwide in the past 5 years (2001–2005) 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% to 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 genera *Norovirus* and *Sapovirus* 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, such as the GII-4 strains identified in USA, Europe, Japan, and Australia in 1995/1996 and again in 2004. 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 (VLPs) morphologically similar to native virus and their incorporation into enzyme immunoassay (EIA) assays.

Pathogenesis

Pathogenesis of NoV and SaV infection is poorly understood as a result of the long-standing inability to adapt these viruses to cell culture, and the absence of a small animal model. 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 three-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. These studies will also be enhanced by discovery of a norovirus that infects mice, and that replicates after transfection of cultured kidney cells.

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. At present the major control strategies for prevention of human calicivirus infection 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 diarrhea in infant mice (EDIM). Similar particles (NCDV) were recognized in 1969 by Mebus and colleagues as a cause of severe diarrhea in newborn calves in Nebraska, USA. Neither virus was considered relevant as a causative agent of severe diarrhea 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 feces from young children admitted to hospital in Melbourne, Australia with severe acute diarrhea. 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 diarrhea in the young of many mammalian and avian species worldwide. Rotavirus enteritis affects all children regardless of socioeconomic status, and results in over 600 000 deaths annually in young children in developing countries.

Classification

Rotaviruses are nonenveloped icosahedral viruses of 70 nm (**Figure 2**) diameter that belong to the genus *Rotavirus*

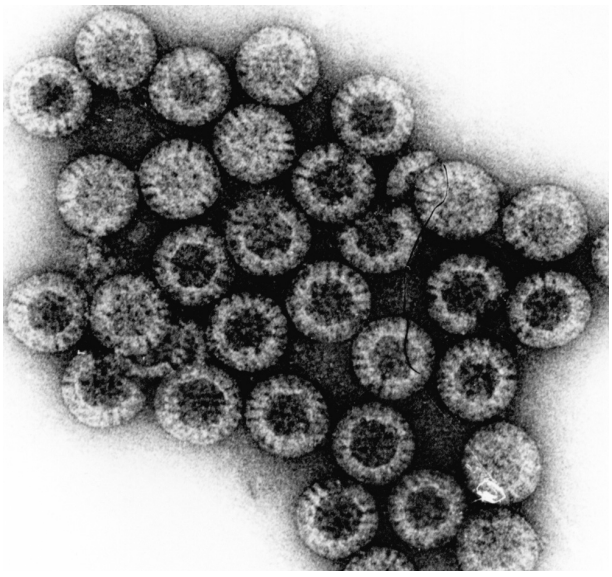

Figure 2 Electron micrograph of negatively stained triple-shelled rotavirus particles in fecal extract.

within the family *Reoviridae*. The double-stranded RNA genome is contained within a triple-layer of viral proteins (VPs) 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. The majority of human and mammalian infections, due to group A viruses, are further classified into serotypes by antigenic differences on VP7 (G-serotypes) and into genotypes by genetic differences on VP4 (P-genotypes). To date there are at least 11 of 15 G-serotypes and 15 of 26 P-genotypes identified in humans. Groups B and C have been identified infrequently in humans. Groups D to G have been identified only in nonhuman mammalian or avian species.

Geographic and Seasonal Distribution

Five rotavirus serotypes G1P[8], G3P[8], G4P[8], G2P[4], and G9P[8] have been the most common serotypes 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.

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 two 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 fecal–oral route, or via aerosols. Rotaviruses replicate in the cytoplasm of mature nonreplicating enterocytes lining the upper portions of the small intestinal villi, eventually causing cytolysis. Profuse watery diarrhea 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 nonstructural 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 diarrhea 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 hospitalization 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. Neutralizing 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 importance of rotavirus disease worldwide and its contribution to childhood mortality in developing countries has resulted in strong initiatives, supported by the World Health Organization, to develop live oral rotavirus vaccines to be administered to infants before 3 months of age. Two contrasting vaccines, a single attenuated G1P[8] human rotavirus and a pentavalent human–bovine G1-G4,P[8] reassortant vaccine, have been proved to be safe and effective in preventing severe rotavirus disease. Both have the potential to radically change global childhood mortality and morbidity.

Adenovirus

History and Classification

Adenoviruses were first detected in 1953 in cultured fragments of tonsillar and adenoidal tissue from children. They are nonenveloped 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 subgenera A–F representing more than 50 serotypes, *Aviadenovirus* (birds), and a newly recognized genus *Atadenovirus* identified in sheep and reptiles. Most are readily cultivatable. Adenovirus infections occur worldwide in many mammalian species, are species specific, usually associated with disease in the respiratory, urinary, and ocular systems, and are frequently shed in feces 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 subgenus group F. Cultivation of EAd remains difficult. The most reliable growth has been achieved in human embryonic kidney cells (293 cells) immortalized by transfection with regions of Ad5.

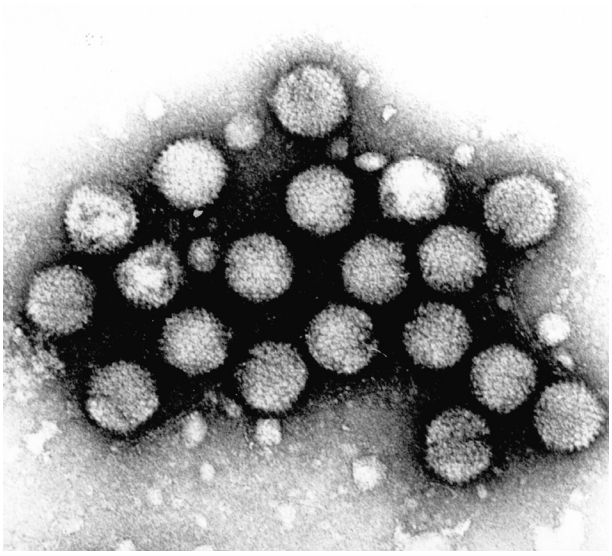

Figure 3 Electron micrograph of negatively stained 'enteric' adenovirus particles (showing characteristic hexagonal shape) in fecal extract. Courtesy of professor M. Studdert.

Geographic and Seasonal Distribution

EAd40 and EAd41 occur worldwide, causing severe acute enteritis in 5–15% of hospitalized 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 kbp DNA. Virus capsomers are arranged as hexons, the corners of which have antenna-like (fiber) projections presumed involved in cell attachment. The DNA genomes of groups A–F are genetically diverse, and differences can be illustrated by analysis using genome restriction endonucleases. The heterogenous genome in groups A–F makes recombination between subgenera unlikely, with exception of groups A and F which show a close evolutionary relationship.

Diagnoses of EAd infection rely on EIA that detects the hexon antigen common to groups A–F, followed by determination of restriction enzyme patterns and/or reactions in EIA incorporating neutralizing, 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 diarrhea are not clear, but destruction of infected epithelial cells has a role.

Clinical Features

Adenovirus diarrhea is more common in infants <12 months old than in older children, and can be protracted with a mean duration of 12 days. Adenovirus diarrhea occurs in immunocompromised patients. Nonseasonal epidemics of EAd diarrhea 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 viremia 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 diarrhea in newborn babies in an obstetric hospital nursery. Astroviruses are small, round nonenveloped 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 diarrhea. There are currently eight serotypes of human astrovirus, designated HAstV 1–8, based on reactivity with polyclonal antisera. HAstV 1 is most common worldwide.

Prevalence rates as a cause of diarrhea vary from 2% to 16% (hospital-based studies), and 5% to 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 diarrhea (lasting for 14 days or more) in children in Bangladesh. Astroviruses are widespread in developed countries, causing outbreaks in day-care centers, hospitals, and nursing homes for the elderly. They are an important cause of enteritis in immunocompromised patients.

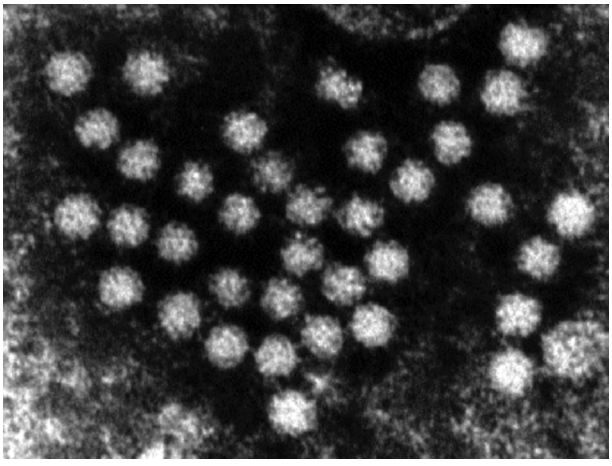

Figure 4 Electron micrograph of negatively stained astrovirus particles (showing star-shape) in fecal extract.

Genetics and Evolution

The HAst genome is a polyadenylated plus-stranded RNA molecule of approximately 7 kbp. The genome contains two open reading frames (ORFs), ORF1a and -1b, code for nonstructural proteins and ORF2 encodes for the capsid protein. Genetic diversity 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 diarrheal feces.

Pathogenesis

Acute astrovirus infection induces a mild watery diarrhea 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 diarrhea. Experimental models of astrovirus enteritis in turkeys and in gnotobiotic lambs show mild histopathological changes in the intestine (despite high mortality from severe osmotic diarrhea) together with viremia. 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 HAstV infection in humans. Cultivation of HAstV 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 diarrhea, 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 fecal–oral and due to virus lability may require close contact. Coronaviruses and toroviruses have been implicated in human diarrheal disease but there is still no consensus about their importance. Similar particles have been seen frequently in children without diarrhea, 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 diarrhea 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 diarrhea 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 diarrhea 24–72 h later. Breda virus also replicates in crypt cells.

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.

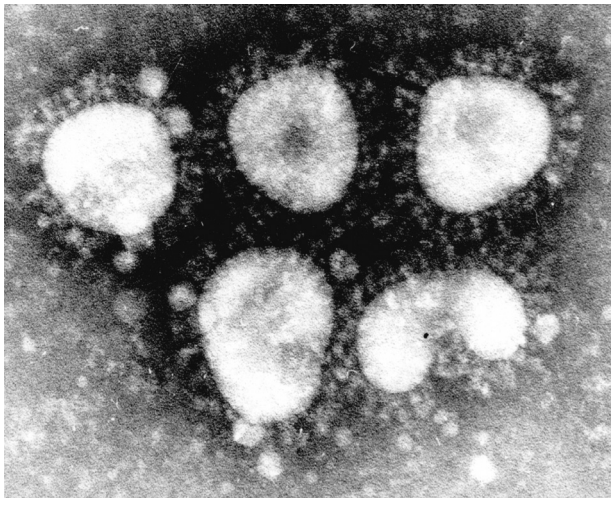

Figure 5 Electron micrograph showing large fringed pleomorphic coronavirus particles (with adherent antibody) in fecal extract.

Picornaviruses

Picornaviruses are 24–30 nm featureless spherical particles containing single-stranded positive-sense RNA. They 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 *Picornavirideae* 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 viremia 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 feces 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 feces 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 diarrhea than those without diarrhea. Their role in gastroenteritis in healthy individuals remains unknown.

See also: Astroviruses; Birnaviruses; Enteroviruses: Human Enteroviruses Numbered 68 and Beyond.

Further Reading

Atmar RL and Estes MK (2001) Diagnosis of noncultivable gastroenteritis viruses, the human caliciviruses. *Clinical Microbiology Reviews* 14: 15–37.

Bresee 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. Novartis Foundation Symposium*, p. 238. New York: Wiley.

Chiba S, Estes MK, Nakata S and Calisher CH (eds.) (1996) *Viral gastroenteritis. Archives of Virology* (supplement 12): 119–128.

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,* vol. 128, pp. 192–217. Chichester: Wiley.

Hansman GS, Oka T, Katayami K, and Takeda N (2007) Human Sapovirus: Genetic diversity, recombination and classification. *Reviews in Medical Virology* 17: 133–141.

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 Reviews 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.

Enteroviruses of Animals

L E Hughes and M D Ryan, University of St. Andrews, St. Andrews, UK

Introduction

In the 1950s, the use of monkey kidney cell cultures for the growth of poliovirus revealed the presence of simian viruses and further study showed some of these to have properties consistent with enteroviruses. In parallel, investigations of viruses infecting domestic animals also revealed the presence of enteroviruses (and enterovirus-like particles) in pigs and cattle. Enteroviruses have since been isolated from African buffalo, water buffalo, sheep, goat, deer, and impala and many have been shown to be related to bovine enterovirus isolates.

In the past, the classification of enteroviruses was primarily based upon the physico-chemical properties of virions, growth in tissue-cultured cell lines, and by serotyping. In practice, this can be difficult with some isolates being poorly recognized by the reference antisera, or, the occurrence of (misleading) cross-reactivities between serotypes. The expansion of the sequence database together with more sensitive cloning/sequencing techniques have facilitated the elucidation of the genome structures of many picornaviruses. Such analyses have replaced other techniques in the classification of picornaviruses, and this article discusses characteristics which are important for the classification of animal enteroviruses.

Animal Enteroviruses

Bovine Enteroviruses

Bovine enteroviruses (BEVs) are endemic in cattle in many regions of the world with infection typically