Non-enveloped RNA viruses

Picornaviridae:

Other Enteroviruses

In view of the difficulty in classifying many enteroviruses, all new isolates have been given a simple numerical designation since 1969.

Enterovirus 70 is the main cause of acute hemorrhagic conjunctivitis, characterized by petechial hemorrhages on the bulbar conjunctivas. Complete recovery usually occurs, and there is no therapy.

Enterovirus 71 is one of the leading causes of viral central nervous system disease, including meningitis, encephalitis, and paralysis. It also causes diarrhea, pulmonary hemorrhages, hand-foot-and-mouth disease, and herpangina. Enterovirus 72 is hepatitis A virus.

Rhinoviruses

Disease; These viruses are the main cause of the common cold.

Important Properties

There are **more than 100 serologic types.** They **replicate better at 33°C** than at 37°C, which explains why they affect primarily the nose and conjunctiva rather than the lower respiratory tract. Because they are **acid-labile,** they are killed by gastric acid when swallowed. This explains why they do not infect the gastrointestinal tract, unlike the enteroviruses. The host range is limited to humans and chimpanzees.

Summary of Replicative Cycle; Replication is similar to that of poliovirus. The cell surface receptor for rhinoviruses is ICAM-1, an adhesion protein located on the surface of many types of cells.

Transmission & Epidemiology

There are **two modes** of transmission for these viruses. In the past, it was accepted that they were transmitted directly from person to person via aerosols of respiratory droplets. However, now it appears that an indirect mode, in which respiratory droplets are deposited on the hands or on a surface such as a table and then transported by fingers to the nose or eyes, is also important.

The common cold is reputed to be the most common human infection, although data are difficult to obtain because it is not a well-defined or notifiable disease. Millions of days of work and school are lost each year as a result of "colds." Rhinoviruses occur worldwide, causing disease particularly in the fall and winter. The reason for this seasonal variation is unclear. Low temperatures per se do not predispose to the common cold, but the crowding that occurs at schools, e.g., may enhance transmission during fall and winter. The frequency of colds is high in childhood and tapers off during adulthood, presumably because of the acquisition of immunity.

A few serotypes of rhinoviruses are prevalent during one season, only to be replaced by other serotypes during the following season. It appears that the population builds up immunity to the prevalent serotypes but remains susceptible to the others.

Pathogenesis & Immunity; The portal of entry is the upper respiratory tract, and the infection is limited to that region. Rhinoviruses rarely cause lower respiratory tract disease, probably because they grow poorly at 37°C. Immunity is serotype-specific and is a function of nasal secretory IgA rather than humoral antibody.

Clinical Findings

After an incubation period of 2 to 4 days, sneezing, nasal discharge, sore throat, cough, and headache are common. A chilly sensation may occur, but there are few other systemic symptoms. The illness lasts about 1 week. Note that other viruses such as coronaviruses, adenoviruses, influenza C virus, and Coxsackie viruses also cause the common cold syndrome.

Laboratory Diagnosis; Diagnosis can be made by isolation of the virus from nasal secretions in cell culture, but this is rarely attempted. Serologic tests are not done.

Treatment & Prevention; No specific antiviral therapy is available. Vaccines appear impractical because of the large number of serotypes. Paper tissues impregnated with a combination of citric acid (which inactivates rhinoviruses) and sodium lauryl sulfate (a detergent that inactivates enveloped viruses such as influenza virus and respiratory syncytial virus) limit transmission when used to remove viruses from fingers contaminated with respiratory secretions. High doses of vitamin C have little ability to prevent rhinovirus-induced colds. Lozenges containing zinc gluconate are available for the treatment of the common cold, but their efficacy remains unproved.

Caliciviruses:

Caliciviruses are small, nonenveloped viruses with single-stranded RNA of positive polarity. Although they share those features with picornaviruses, caliciviruses are distinguished from picornaviruses by having a larger genome and having distinctive spikes on the surface. Norwalk virus is the main human pathogen in the calicivirus family.

Norwalk Virus (Norovirus)

Disease; Norwalk virus (also known as Norovirus) is one of the most common causes of viral gastroenteritis in adults both in the United States and worldwide. It is named for an outbreak of gastroenteritis in a school in Norwalk, OH, in 1969.

Important Properties; Norwalk virus has a nonsegmented, single-stranded, positive-polarity RNA genome. It is a nonenveloped virus with an icosahedral nucleocapsid. There is no virion polymerase. In the electron microscope, 10 prominent spikes and 32 cup-shaped depressions can be seen. The number of serotypes is uncertain.

Summary of Replicative Cycle; Norwalk virus has not been grown efficiently in cell culture, so its replicative cycle has been difficult to study. It is presumed to replicate in a manner similar to that of picornaviruses.

Transmission & Epidemiology; Norwalk virus is transmitted by the fecal–oral route, often involving the ingestion of contaminated seafood or water. Outbreaks typically occur in group settings such as cruise ships (especially in the Caribbean region), schools, camps, hospitals, and nursing homes. Person-to-person transmission also occurs, especially in group settings. There are many animal caliciviruses, but there is no evidence that they cause human infection.Infection is enhanced by several features of the virus: low infectious dose, excretion of virus in the stool for several weeks after recovery, and resistance to inactivation

by chlorination and to drying in the environment. It is thought to remain infectious for several days on environmental surfaces such as door handles.

Pathogenesis & Immunity; Norwalk virus infection is typically limited to the mucosal cells of the intestinal tract. Watery diarrhea without red cells or white cells occurs. Many asymptomatic infections occur, as determined by the detection of antibodies. Immunity following infection appears to be brief and reinfection can occur.

Clinical Findings; Disease is characterized by sudden onset of vomiting and diarrhea accompanied by low-grade fever and abdominal cramping. Neither the emesis nor the stool contain blood. The illness typically lasts several days and there are no long-term sequelae, except in certain immunocompromised patients in whom a prolonged infection can occur. In some outbreaks, certain patients manifest signs of central nervous system involvement such as headache, meningismus, photophobia, and obtundation.

Laboratory Diagnosis; The diagnosis is primarily a clinical one. A polymerase chain reaction (PCR)-based test on the stool is performed primarily when there are public health implications.

Treatment & Prevention; There is no antiviral therapy or vaccine available. Dehydration and electrolyte imbalance caused by the vomiting and diarrhea may require intravenous fluids. Personal hygiene, such as handwashing, and public health measures, such as proper sewage disposal, are helpful.

Reoviruses: REO is an acronym for *r*espiratory *e*nteric *o*rphan; when the virus was discovered, it was isolated from the respiratory and enteric tracts and was not associated with any disease. Rotaviruses are the most important human pathogens in the reovirus family.

Rotavirus; Disease: Rotavirus is the most common cause of viral gastroenteritis in young children.

Important Properties; Rotavirus has a **segmented, double-stranded RNA genome** surrounded by a double-layered icosahedral capsid without an envelope. The rotavirus genome has 11 segments. The virion contains an **RNA-dependent RNA polymerase.** A virion polymerase is required because human cells do not have an RNA polymerase that can synthesize mRNA from a double-stranded RNA template.

Many domestic animals are infected with their own strains of rotaviruses, but these are not a source of human disease. There are at least six serotypes of human rotavirus. The outer surface protein (also known as the viral hemagglutinin) is the type-specific antigen and elicits protective antibody.

Summary of Replicative Cycle; Rotavirus attaches to the cell surface at the site of the -adrenergic receptor. After entry of the virion into the cell, the RNA-dependent RNA polymerase synthesizes mRNA from each of the 11 segments within the cytoplasm. The 11 mRNAs are translated into the corresponding number of structural and nonstructural proteins. One of these, an RNA polymerase, synthesizes minus strands that will become part of the genome of the progeny virus. Capsid proteins form an incomplete capsid around the minus strands, and then the plus strands of the progeny genome segments are synthesized. The virus is released from the cytoplasm by lysis of the cell, not by budding.

Transmission & Epidemiology; Rotavirus is transmitted by the **fecal–oral** route. Infection occurs worldwide, and by age 6 years most children have antibodies to at least one serotype.

Pathogenesis & Immunity; Rotavirus replicates in the mucosal cells of the small intestine, resulting in the excess secretion of fluids and electrolytes into the bowel lumen. The consequent loss of salt, glucose, and water leads to diarrhea. No inflammation occurs, and the diarrhea is non bloody. It is thought that this watery diarrhea is caused primarily by stimulation of the enteric nervous system.

It is likely that intestinal IgA directed against specific serotypes protects against reinfection and that colostrum IgA protects newborns up to the age of 6 months.

Clinical Findings; Rotavirus infection is characterized by nausea, vomiting, and watery, non-bloody diarrhea. **Gastroenteritis** is most serious in **young children,** in whom dehydration and electrolyte imbalance are a major concern. Adults usually have minor symptoms.

Laboratory Diagnosis; Although the diagnosis of most cases of viral gastroenteritis does not involve the laboratory, a diagnosis can be made by **detection of rotavirus in the stool** by using radioimmunoassay or ELISA. This approach is feasible because there are large numbers of virus particles in the stool. The original demonstration of rotavirus in the stool was done by immunoelectron microscopy, in which antibody aggregated the virions, allowing them to be visualized in the electron microscope. This technique is not feasible for routine clinical use. In addition to antigen detection, the diagnosis can be made by observation of a fourfold or greater rise in antibody titer. Although the virus can be cultured, this procedure is not routinely done.

Treatment & Prevention; There are two rotavirus vaccines available. Both contain live virus and are given orally. One is a live attenuated vaccine (Rotarix), which contains the single most common rotavirus serotype (G1) causing disease in the USA. The other is a live reassortant vaccine (Rotateq), which contains five rotavirus strains.The five rotaviruses in the Rotateq vaccine are reassortants in which the gene for the human outer surface protein is inserted into a bovine strain of rotavirus. (Recall that rotavirus has a segmented genome.) The bovine strain is nonpathogenic for humans, but the human outer surface protein in the vaccine virus elicits protective (IgA) immunity in the GI tract.

A previously approved vaccine (Rotashield) was withdrawn when a high rate of intussusception occurred in vaccine recipients. Hygienic measures such as proper sewage disposal and handwashing are helpful. There is no antiviral therapy.

Features of Viruses that Infect the Respiratory Tract[1]						
Virus	**Disease**	**Number of Serotypes**	**Lifelong Immunity to Disease**	**Vaccine Available**	**Viral Latency**	**Treatment**
RNA viruses						
Influenza virus	Influenza	Many	No	+	–	Amantadine rimantadine, oseltamivir, zanamivir
Parainfluenza virus	Croup	Many	No	–	–	None
Respiratory syncytial virus	Bronchiolitis	Two	Incomplete	–	–	Ribavirin
Rubella virus	Rubella	One	Yes	+	–	None
Measles virus	Measles	One	Yes	+	–	None
Mumps virus	Parotitis, meningitis	One	Yes	+	–	None
Rhinovirus	Common cold	Many	No	–	–	None
Coronavirus	Common cold, SARS[2]	Three	No	–	–	None
Coxsackie virus	Herpangina, pleurodynia, myocarditis	Many	No	–	–	None
DNA viruses						
Herpes simplex virus type 1	Gingivostomatitis	One	No	–	+	Acyclovir in immunodeficient patients
Epstein-Barr virus	Infectious mononucleosis	One	Yes	–	+	None
Varicella-zoster virus	Chickenpox, shingles	One	Yes[3]	–	+	Acyclovir in immunodeficient patients
Adenovirus	Pharyngitis, pneumonia	Many	No	+[4]	+	None

[1]Influenza virus, parainfluenza virus, respiratory syncytial virus, rubella virus, measles virus, mumps virus, and coronavirus are enveloped RNA viruses.

[2]SARS is severe acute respiratory syndrome.

[3]Lifelong immunity to varicella (chickenpox) but not to zoster (shingles).

[4]For military recruits only.

Clinical Features of Certain RNA Enveloped Viruses				
Virus	**Rash Occurs**	**Giant Cells Formed**	**Type of Vaccine**	**Immune Globulins Commonly Used**
Influenza	No	No	Killed	No
Respiratory syncytial	No	Yes	None	No
Measles	Yes	Yes	Live	No
Rubella	Yes	No	Live	No
Rabies	No	No	Killed	Yes

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