Non-enveloped RNA viruses

Picornaviruses:

Picornaviruses are small (20–30 nm) **nonenveloped** viruses composed of an **icosahedral nucleocapsid** and a **single-stranded** RNA genome. The genome RNA has positive polarity, i.e., on entering the cell; it functions as the viral mRNA. The genome RNA is unusual because it has a protein on the 5' end that serves as a primer for transcription by RNA polymerase. Picornaviruses replicate in the cytoplasm of cells. They are not inactivated by lipid solvents, such as ether, because they do not have an envelope.

The picornavirus family includes two groups of medical importance: the **enteroviruses** and the **rhinoviruses.** Among the major enteroviruses are poliovirus, Coxsackie viruses, echoviruses, and hepatitis A virus. Enteroviruses infect primarily the enteric tract, whereas rhinoviruses are found in the nose and throat (rhino = nose).

Important features of viruses that commonly infect the intestinal tract are summarized in Table –1. Enteroviruses replicate optimally at 37°C, whereas rhinoviruses grow better at 33°C, in accordance with the lower temperature of the nose. Enteroviruses are stable under acid conditions (pH 3–5), which enables them to survive exposure to gastric acid, whereas rhinoviruses are acid-labile. This explains why rhinovirus infections are restricted to the nose and throat.

Table –1 Features of Viruses Commonly Infecting the Intestinal Tract

Virus	**Nucleic Acid**	**Disease**	**Number of Serotypes**	**Lifelong Immunity to Disease**	**Vaccine Available**	**Antiviral Therapy**
Poliovirus	RNA	Poliomyelitis	3	Yes (type-specific)	+	–
Echoviruses	RNA	Meningitis, etc	Many	No	–	–
Coxsackie viruses	RNA	Meningitis, carditis, etc	Many	No	–	–
Hepatitis A virus (enterovirus 72)	RNA	Hepatitis	1	Yes	+	–
Rotavirus	RNA	Diarrhea	Several[1]	No	–[2]	–
Norwalk virus (Norovirus)	RNA	Diarrhea	Unknown	No	–	–
Adenovirus	DNA	Diarrhea	40,41; of which 2 cause diarrhea	Unknown	–	–

[1]Exact number uncertain.

[2]Rotavirus vaccine was released but was withdrawn because of side effects (see text).

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Enteroviruses

Poliovirus;This virus causes poliomyelitis.

The host range is limited to primates, i.e., humans and nonhuman **primates** such as apes and monkeys. This limitation is due to the binding of the viral capsid protein to a receptor found only on primate cell membranes. However, note that purified viral RNA (without the capsid protein) can enter and replicate in many nonprimate cells—the RNA can bypass the cell membrane receptor, i.e., it is "infectious RNA."

There are **three serologic (antigenic) types** based on different antigenic determinants on the outer capsid proteins. Because there is little cross-reaction, protection from disease requires the presence of antibody against each of the three types.

Summary of Replicative Cycle; The virion interacts with specific cell receptors on the cell membrane and then enters the cell. The capsid proteins are then removed. After uncoating, the genome RNA functions as mRNA and is translated into **one very large polypeptide** called noncapsid viral protein 00. This polypeptide is cleaved by a virus-encoded protease in multiple steps to form both the capsid proteins of the progeny virions and several noncapsid proteins, including the RNA polymerase that synthesizes the progeny RNA genomes. Replication of the genome occurs by synthesis of a complementary negative strand, which then serves as the template for the positive strands. Some of these positive strands function as mRNA to make more viral proteins, and the remainder become progeny virion genome RNA. Assembly of the progeny virions occurs by coating of the genome RNA with capsid proteins. Virions accumulate in the cell cytoplasm and are released upon death of the cell. They do not bud from the cell membrane.

Transmission & Epidemiology; Poliovirus is transmitted by the **fecal–oral** route. It replicates in the oropharynx and intestinal tract. Humans are the only natural hosts.

As a result of the success of the vaccine, poliomyelitis caused by naturally occurring "wild-type" virus has been **eradicated** from the United States and, indeed, **from the entire Western hemisphere.** The rare cases in the United States occur mainly in (1) people exposed to virulent revertants of the attenuated virus in the live vaccine and (2) unimmunized people exposed to "wild-type" poliovirus while traveling abroad. Before the vaccine was available, epidemics occurred in the summer and fall.

Pathogenesis & Immunity: After replicating in the oropharynx and small intestine, especially in lymphoid tissue, the virus spreads through the bloodstream to the central nervous system. It can also spread retrograde along nerve axons.

In the central nervous system, poliovirus preferentially replicates in the **motor neurons** located in the **anterior horn** of the spinal cord. Death of these cells results in paralysis of the muscles innervated by those neurons. Paralysis is not due to virus infection of muscle cells. The virus also affects the brain stem, leading to "bulbar" poliomyelitis (with respiratory paralysis), but rarely damages the cerebral cortex.

In infected individuals, the immune response consists of both intestinal IgA and humoral IgG to the specific serotype. Infection provides lifelong type-specific immunity.

Clinical Findings

The range of responses to poliovirus infection includes (1) inapparent, asymptomatic infection, (2) abortive poliomyelitis, (3) nonparalytic poliomyelitis, and (4) paralytic poliomyelitis. Asymptomatic infection is quite common. Roughly 1% of infections are clinically apparent. The incubation period is usually 10 to 14 days.

The most common clinical form is abortive poliomyelitis, which is a mild, febrile illness characterized by headache, sore throat, nausea, and vomiting. Most patients recover spontaneously. Nonparalytic poliomyelitis manifests as aseptic meningitis with fever, headache, and a stiff neck. This also usually resolves spontaneously. In paralytic poliomyelitis, flaccid paralysis is the predominant finding, but brain stem involvement can lead to life-threatening respiratory paralysis. Painful muscle spasms also occur. The motor nerve damage is permanent, but some recovery of muscle function occurs as other nerve cells take over. In paralytic polio, both the meninges and the brain parenchyma (meningoencephalitis) are often involved. If the spinal cord is also involved, the term meningomyeloencephalitis is often used.

Laboratory Diagnosis: The diagnosis is made either by isolation of the virus or by a rise in antibody titer. Virus can be recovered from the throat, stool, or spinal fluid by inoculation of cell cultures. The virus causes a cytopathic effect (CPE) and can be identified by neutralization of the CPE with specific antisera.

Treatment; There is no antiviral therapy. Treatment is limited to symptomatic relief and respiratory support, if needed. Physiotherapy for the affected muscles is important.

Prevention; Poliomyelitis can be prevented by both the **killed** vaccine (Salk vaccine, inactivated vaccine, IPV) and the **live, attenuated** vaccine (Sabin vaccine, oral vaccine, OPV) (Table –2). Both vaccines induce humoral antibodies, which neutralize virus entering the blood and hence prevent central nervous system infection and disease. Both the killed and the live vaccines contain all three serotypes. At present, the **inactivated vaccine** is preferred for reasons that are described below.

Table –2 Important Features of Poliovirus Vaccines

Attribute	**Killed (Salk)**	**Live (Sabin)**
Prevents disease	Yes	Yes
Interrupts transmission	No	Yes
Induces humoral IgG	Yes	Yes
Induces intestinal IgA	No	Yes
Affords secondary protection by spread to others	No	Yes
Interferes with replication of virulent virus in gut	No	Yes
Reverts to virulence	No	Yes (rarely)
Coinfection with other enteroviruses may impair immunization	No	Yes
Can cause disease in the immunocompromised	No	Yes
Route of administration	Injection	Oral
Requires refrigeration	No	Yes
Duration of immunity	Shorter	Longer

The duration of immunity is thought to be longer with the live than with the killed vaccine, but a booster

dose is recommended with both.

The currently approved vaccine schedule consists of four doses of inactivated vaccine administered at 2 months, 4 months, 6 to 18 months, and upon entry to school at 4 to 6 years. One booster (lifetime) is recommended for adults who travel to endemic areas. The use of the inactivated vaccine should prevent some of the approximately 10 cases per year of vaccine-associated paralytic polio that arise from reversion of the attenuated virus in the vaccine.

Passive immunization with immune serum globulin is available for protection of unimmunized individuals known to have been exposed. Passive immunization of newborns as a result of passage of maternal IgG antibodies across the placenta also occurs.

Coxsackie Viruses

Coxsackie viruses are named for the town of Coxsackie, NY, where they were first isolated.

Diseases;Coxsackie viruses cause a variety of diseases. Group A viruses cause, for example, herpangina, acute hemorrhagic conjunctivitis, and hand-foot-and-mouth disease, whereas group B viruses cause pleurodynia, myocarditis, and pericarditis. Both types cause nonspecific upper respiratory tract disease (common cold), febrile rashes, and aseptic meningitis. Coxsackie viruses and echoviruses together cause approximately 90% of cases of viral (aseptic) meningitis.

Important Properties; Group classification is based on pathogenicity in mice. Group A viruses cause widespread myositis and flaccid paralysis, which is rapidly fatal, whereas group B viruses cause generalized, less severe lesions of the heart, pancreas, and central nervous system and focal myositis. At least 24 serotypes of Coxsackie virus A and 6 serotypes of Coxsackie virus B are recognized.

The size and structure of the virion and the nature of the genome RNA are similar to those of poliovirus. Unlike poliovirus, they can infect mammals other than primates.

Summary of Replicative Cycle; Replication is similar to that of poliovirus.

Transmission & Epidemiology

Coxsackie viruses are transmitted primarily by the **fecal–oral** route, but respiratory **aerosols** also play a role. They replicate in the oropharynx and the intestinal tract. Humans are the only natural hosts. Coxsackie virus infections occur worldwide, primarily in the summer and fall.

Pathogenesis & Immunity; Group A viruses have a predilection for skin and mucous membranes, whereas group B viruses cause disease in various organs such as the heart, pleura, pancreas, and liver. Both group A and B viruses can affect the meninges and the motor neurons (anterior horn cells) to cause paralysis. From their original site of replication in the oropharynx and gastrointestinal tract, they disseminate via the blood stream. Immunity following infection is provided by type-specific IgG antibody.

Clinical Findings; Group a—Specific Diseases

Herpangina is characterized by fever, sore throat, and tender vesicles in the oropharynx. **Hand-foot-and-mouth disease** is characterized by a vesicular rash on the hands and feet and ulcerations in the mouth, mainly in children.

Group B—Specific Diseases

Pleurodynia (Bornholm disease, epidemic myalgia, "devil's grip") is characterized by fever and severe pleuritic-type chest pain. Note that pleurodynia is pain due to an infection of the intercostal muscles not of the pleura.

Myocarditis and pericarditis are characterized by fever, chest pain, and signs of congestive failure. Dilated cardiomyopathy with global hypokinesia of the myocardium is a feared sequel that often requires cardiac transplantation to sustain life. **Diabetes** in mice can be caused by pancreatic damage as a result of infection with Coxsackie virus B4. This virus is suspected to have a similar role in juvenile diabetes in humans.

Diseases Caused by Both Groups; Both groups of viruses can cause **aseptic meningitis,** mild paresis, and acute flaccid paralysis similar to poliomyelitis. Upper respiratory infections and minor febrile illnesses with or without rash can occur also.

Laboratory Diagnosis

The diagnosis is made either by isolating the virus in cell culture or suckling mice or by observing a rise in titer of neutralizing antibodies. A rapid (2.5 hour) PCR-based test for enteroviral RNA in the spinal fluid is useful for making a prompt diagnosis of viral meningitis because culture techniques typically take days to obtain a result.

Treatment & Prevention; There is neither antiviral drug therapy nor a vaccine available against these viruses. No passive immunization is recommended.

Echoviruses

- The first echoviruses were accidentally discovered in human feces, unassociated with human disease during epidemiological studies of polioviruses. The viruses were named echoviruses (enteric, cytopathic, human, orphan viruses).
- These viruses were produced CPE in cell cultures, but did not induce detectable pathological lesions in suckling mice.
- Altogether, There are 32 echoviruses

Diseases associated with Enteroviruses

Syndrome	Polio	Cox A	Cox B	Echo
Paralytic disease	+	+	+	+
Meningitis-encephalitis	+	+	+	+
Carditis	+	+	+	+
Neonatal disease	-	-	+	+
Pleurodynia	-	-	+	-
Herpangina	-	+	-	-
Rash disease	-	+	+	+
Haemorr. conjunctivitis	-	+	-	-
Respiratory infections	+	+	+	+
Undifferentiated fever	+	+	+	+
Diabetes/pancreatitis	-	-	+	-