GENERAL CHARACTERISTICS

- Viruses are small, obligatory intracellular parasites. Viruses pass through filters that retain bacteria.
- Viruses are true parasites in that they contain no mitochondria, ribosomes, or other cellular organelles of their own. They depend entirely on the machinery of the host cell for their energy production and protein synthesis. Viruses do not grow in nutrient media (unlike bacteria).
- All cells or microorganisms contain both DNA and RNA, with the repository of the genetic material being DNA. Viruses, however, have either DNA or RNA, but never both. The nucleic acid present in the virus is the genetic material of the particular virus.
- Viruses are not sensitive to antibiotics because their metabolism is completely dependent on the host cell.
- Interferon can be induced and inhibit viral replication. Some viruses block induction of interferon.

PHYSICAL STRUCTURE OF VIRUSES

VIRUSES vary tremendously in shape and size, but all viruses are composed of two essential components: protein and nucleic acid. Some viruses also contain lipid membranes surrounding the nucleic acid.
CLASSIFICATION OF VIRUSES

Today, the standard classification system is by the viral genetic information or genome. Viruses may contain RNA or DNA which may be either single-stranded or double-stranded. These strands may be linear or circular. The viral genome may be segmented (there may be separate pieces of nucleic acid in the viral particle).

- **genome:** RNA or DNA
  - if RNA, type (+ or - polarity)
  - single or double-stranded
  - nonsegmented or segmented
  - molecular weight

**Genome polarity:**
Viruses containing single-stranded RNA may be of - or + polarity. RNA of - polarity cannot be translated directly into protein. The RNA must first be transcribed into mRNA. This process creates a complimentary strand of RNA, (referred to as + sense or + polarity) which can be translated into protein. Viruses with - sense genomic RNA must carry their own enzyme which transcribes RNA into a complimentary strand of RNA (enzyme: RNA-dependent RNA polymerase, example: paramyxoviruses).

**Naming viruses:**

- **Family:** -viride. Example: Paramyxoviridae
- **Genus:** -virus. Example: Morbillivirus
- **Species:** vernacular. Example: Measles

You should know the family names and species name for each virus. Knowing the family of a virus will help you understand why common clinical approaches are appropriate for seemingly distinct diseases. For example, the use of acyclovir to treat chicken pox and genital herpes, both viruses are in the Herpesviridae and replicate using similar mechanisms. The DNA polymerases of these viruses can be inhibited by acyclovir.
VIRAL REPLICATION

SEQUENTIAL STAGES OF VIRUS INFECTION

We focus on understanding each of these steps so that we can design anti-viral drugs to block virus infection/replication/or virion production without interfering with the viability of the host cell.

Attachment - Virus protein binds to specific plasma membrane receptor. Attachment to a specific receptor often determines the tropism of the virus.

Penetration - Most viruses are taken up in coated pits which form vesicles.

Uncoating - Virus envelope fuses with endosomes (or lysosome) membrane at low pH.

Transcription - Viral mRNA is synthesized.

Translation - Viral mRNAs are translated into proteins. The transport of membrane-associated proteins is done by the cell.

Replication - Genome replication is specific for each type of viral genome (DNA, RNA, reverse transcription, etc.)

Assembly - Components of the virion are self-assembling.

Release - Enveloped viruses bud through the cell membrane (plasma, ER or nuclear). Naked viruses are released when the cell lyses.

These stages are important because each one is a potential target for anti-viral therapy. If we can identify unique steps in viral replication, we may be able to design specific blockers/inhibitors.
HOST IMMUNE RESPONSE TO VIRAL INFECTION

INTERFERON
Interferon synthesis is induced by virus infection and double-stranded RNA molecules. Interferon acts like a hormone, on other cells, through a specific receptor. It induces anti-viral state in neighboring, uninfected cells. Interferon is short-lived in the body.

Effects of Interferon:

- inhibition of translation; protein kinase phosphorylates eIF2
- destruction of mRNA, mediated by 2-5A synthetase
- inhibition of protein synthesis

Antibody Response
- Detection of IgM specific to the virus during the acute stage of illness is frequently used in diagnosis. Detection of IgG specific to the virus is a good indicator of previous exposure to the virus.

Cell-mediated Immunity
- Very important in the control of latent viral infection (especially herpesviruses). Loss of CMI in chemotherapy or transplant patients results in activation of latent viral infections.
POLIOVIRUS & POLIOMYELITIS

INTRODUCTION

*Picornaviridae* is one the largest families of viruses and include many important human pathogens such as poliovirus, rhinovirus, Hepatitis A virus and coxsackie viruses.

![Virus family diagram](image)

**UNIQUE PROPERTIES OF HUMAN PICORNAVIRUSES**

- Naked, small (25 - 30 nm), icosahedral capsid enclosing a single-stand positive (+) RNA genome
- Virus replicates in the cytoplasm. Genome acts as a mRNA and is translated into a polyprotein, which is then cleaved into enzymatic and structural proteins
- Most viruses are cytolytic
- Enteroviruses are resistant to pH 3.0 – pH 9.0, detergents, mild sewage treatment and temperature

**EPIDEMIOLOGY**

- Only humans are infected
- Fecal oral transmission
- Summer-Fall epidemics in temperate climates
- 6-20 day incubation period, communicable up to 6 weeks after infection

**PATHOGENESIS OF POLIOVIRUS INFECTIONS**

**DISEASE MECHANISM OF POLIOVIRUS**

- Poliovirus enters via the intestinal mucosa and infects the underlying lymphatic tissue.
In the absence of serum antibody, poliovirus spreads by viremia to cells of a receptor-bearing target tissue.

The infected target tissue determines the subsequent disease (polio: anterior horn cells).

Viral, rather than immune, pathology is usually responsible for disease symptoms.

Poliovirus is shed into feces for long periods.

Infection is usually asymptomatic or causes mild "flu-like" symptoms.

**CLINICAL SYNDROMES OF POLIOVIRUS INFECTION**

Clinical syndromes vary due to several factors including viral serotype, infecting dose, portal of entry, age, pregnancy and state of health.

**Four Possible Outcomes**

- **Asymptomatic illness** results if the virus is limited to infection of the oropharynx and the gut. At least 90% of poliovirus infections are of the asymptomatic type.

- **Abortive poliomyelitis** (minor illness) is a nonspecific febrile illness occurring in approximately 5% of infected individuals. Symptoms of fever, headache, malaise, sore throat and vomiting occur within 3 to 4 days of exposure.

- **Nonparalytic poliomyelitis or aseptic meningitis** occurs in 1% - 2% of patients with poliovirus infections. The virus progresses into the central nervous system and the meninges, causing back pain and muscle spasms in addition to the symptoms of minor illness.

- **Paralytic polio** occurs in 0.1% - 2.0% of persons with poliovirus infections and is the most severe outcome. Major illness follows 3 to 4 days after minor illness has subsided, thereby producing a biphasic illness. The virus spreads from the blood to the anterior horn cells of the spinal cord and the motor cortex of the brain. The severity of the paralysis is determined by the extent of the neuronal infection and the neurons affected. Spinal paralysis may involve one or more limbs, whereas bulbar (cranial) paralysis may involve a combination of cranial nerves and even the medullary respiratory center.

**Special note:** Post-polio syndrome is consequence of poliomyelitis that may occur much later in life (30 to 40 years) for 20% - 80% of the original victims. These individuals suffer a deterioration of the originally affected muscles. Infectious poliovirus is not present, but the syndrome is believed to be due to a loss of neurons in the initially affected nerves.

**DETECTION OF POLIOVIRUS INFECTION**

Most enterovirus infections are detected by isolation of virus from throat swabs, stool or rectal swabs and sometimes from the cerebrospinal fluid. However, poliovirus is rarely isolated from cerebrospinal fluid. Isolation of an enterovirus from the throat is highly suggestive of an etiologic
association, as the virus is usually detectable at this site for only 2 days to 2 weeks after infection; isolation of virus from fecal specimens only must be interpreted more cautiously, as asymptomatic shedding from the bowel may persist for as long as 4 months. Since poliovirus infections is now rare, suspected cases are usually confirmed by serology with acute and convalescent sera and by direct isolation of virus from at least 2 stool samples. Virus isolates are sequenced to determine the genotype of the paralytic infection.

**PREVENTION**

**POLIOVIRUS VACCINES**

**Salk vaccine** - Contains inactivated poliovirus of all three serotypes. The vaccine was given intramuscularly and little or no duodenal IgA was generated.

**Sabin vaccine** - Live, attenuated vaccine of all three serotypes. It is given orally and induces good duodenal IgA response.

![Graph showing antibody response to polio vaccines](image-url)

**FIGURE 57-10.** Serum and secretory antibody response to intramuscular inoculation of inactivated polio vaccine and to live attenuated oral polio vaccine. Note the presence of secretory IgA induced by the live polio vaccine. (Redrawn from Ogra P et al: Rev Infect Dis 2:352-369 1980. Copyright 1980, University of Chicago Press.)
Function of Antibody

- Secretory antibody response can prevent initiation of infection.
- Serum antibody blocks viremic spread to target tissue, preventing symptoms.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live (oral polio vaccine)</td>
<td>Effective, Lifelong immunity, Induction of secretory antibody response similar to that of natural infection, Spread of attenuated virus circulating to contacts promotes indirect immunization (herd immunity), Inexpensive and easy to administer, No need for repeated booster vaccine</td>
<td>Risk of vaccine-associated poliomyelitis in vaccine recipients or contacts, Spread of vaccine to contacts without their consent, Not safe for administration to immunodeficient patients</td>
</tr>
<tr>
<td>Inactivated polio vaccine</td>
<td>Effective, Good stability during transport and in storage, Safe administration in immunodeficient patients, No risk of vaccine-related disease</td>
<td>Lack of induction of secretory antibody, Booster vaccine needed for lifelong immunity, Requires sterile syringes and needles, Injection more painful than oral administration, Higher community immunization levels needed than with live vaccine</td>
</tr>
</tbody>
</table>

CONSIDERATIONS

- Immunocompromised individuals should not receive any live vaccine
- Contact with infected or vaccinated individuals has a booster effect
- Mutations in the vaccine strains can cause poliomyelitis (this occurs approximately 1/3,000,000 doses and is termed vaccine-associated paralytic polio, VAPP).

2004 Recommendations of the American Academy of Pediatrics

3 Dose Regimen
First Vaccination, IPV
First Boost, IPV
Second Boost, IPV

This vaccination regimen is designed to eliminate VAPP in the United States.

STUDY QUESTIONS

1. Why is it more difficult to design anti-viral drugs as compared to anti-bacterial agents?
2. How are viruses classified? How does this classification help you when new antiviral drugs come on the market?
3. Discuss how interferons differ from antibodies in their origin, specificity, and mode of action in viral infections.
EXAMPLE OF TEST QUESTION

The mechanism of action of interferon involves:

A. Induction of enzymes to degrade mRNA and inhibit protein synthesis
B. Upregulation of the immune response to viral antigens
C. Stimulation of the cycle to cause cells to divide before they are infected
D. Shutdown of splicing activity in the virus infected cells.
E. Killing of virus infected cells by NK cells

ANSWER TO ABOVE QUESTION: A