PHARMACEUTICAL MICROBIOLOGY

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OBJECTIVES

- Viral Replication
- Classification of Viruses
- Enveloped DNA Viruses
  - Herpes Simplex Virus Type 1
  - Herpes Simplex Virus Type 2
  - Varicella zoster Virus
  - Cytomegalovirus
  - Epstein-Barr Virus
  - Human Herpesvirus 8
- Non-Enveloped DNA Viruses
  - Human Papillomavirus
  - Parvovirus B19

Viral Replication

- Viruses do not have their own metabolism and require a host cell to make new products.

- They use the synthesis mechanism, energy and chemical substances of the host cell to reproduce.

- They are totally dependent on a host cell to replicate (make copies of itself).

Viral Replication

Steps in Viral Replication:

1. Adsorption (Attachment):

This is the first step in viral replication. Surface proteins of the virus interact with specific receptors on the target cell's surface. Damage to the binding sites on the virion or blocking by specific antibodies can render virions non-infectious.

2. Penetration: Entry of viral genome (DNA or RNA) into the host cell's cytoplasm.

Viral Replication

Steps in Viral Replication:

3. Eclipse (Replication): Viral nucleic acid is replicated using nucleotides from the host cell. Protein coats are produced using the amino acids of the host cell (Synthesis of new components). In this period, the virus loses its ability to make disease.

4. Assembly: After many copies of viral components are made, they are assembled into complete viruses.

Viral Replication

Steps in Viral Replication:

5. Release:

Naked (non-enveloped) viruses are released from the infected cell by the disruption of the cellular membrane (often by apoptosis= programmed cell death, it can be initiated by virus or host cell).

Enveloped viruses exit their host cell by budding from cellular membrane. Enveloped viruses acquire their lipid envelope from the membranes of host cells.

Viral Replication

- **Viropexis** is the process by which virus binds to host cell and subsequent absorption (engulfment) of virus particle by that cell.
- **Non-enveloped viruses** attach to a specific receptor site on the host cell membrane through attachment proteins in the capsid. Non-enveloped viruses enter the cell through endocytosis.
- **Enveloped viruses** attach to a specific receptor site on the host cell membrane via glycoproteins embedded in the viral envelope (viral envelope fuses with the host cell membrane).

Viral Replication

3 types of RNA can be found in viruses:

- ✓ Positive stranded RNA
- ✓ Negative stranded RNA
- ✓ RNA of the Retroviruses

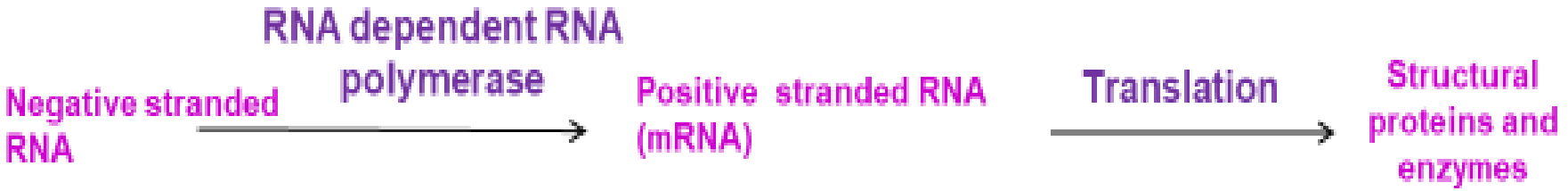
Positive stranded RNA

Positive stranded RNA genome can serve as mRNA and directly translated into protein.

Viral Replication

Negative stranded RNA

Negative stranded RNA viruses have to convert their genomes into mRNA. Negative stranded RNA viruses carry an enzyme called **RNA-dependent RNA polymerase**, which translates the negative strand into a positive strand (mRNA).



Viral Replication

RNA of the Retroviruses

Retroviruses are also single stranded RNA viruses; however, **their genome is converted into double stranded DNA** through **viral reverse transcriptase**.

Viral Replication

- **Negative stranded RNA viruses** have **RNA dependent RNA polymerase** inside virions. Because **this enzyme does not present in human cells.**
- In most viruses, DNA is transcribed into RNA, and then RNA is translated into protein.
- However, **retroviruses** function differently, as their **RNA is reverse-transcribed into DNA**, which is integrated into the host cell's genome (when it becomes a provirus), and then undergoes the usual transcription and translational processes to express the genes carried by the virus.

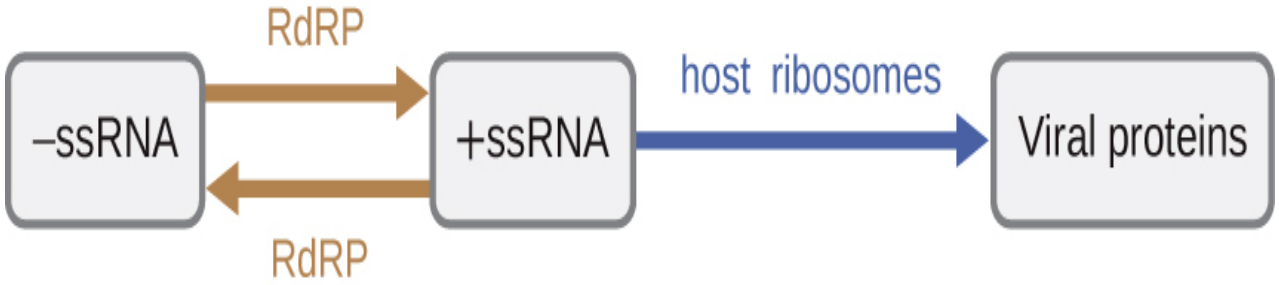
Viral Replication

The information contained in a retroviral gene is thus used to generate the corresponding protein via the sequence:

RNA → DNA → RNA → polypeptide.

Viral Replication

- **Positive stranded RNA** virus can directly cause infection.
- **Negative stranded RNA** virus is not infectious by itself as it needs to be transcribed into positive stranded RNA.



RdRP = viral RNA-dependent RNA polymerase

+ssRNA = positive (+) single strand

–ssRNA = negative (–) single-strand RNA

- **In DNA viruses,** DNA transcribed into mRNA and then mRNA is translated into structural proteins and enzymes.

Classification of Viruses

1. Nucleic Acid

- DNA-RNA
- Single-stranded (ss)-Double stranded (ds)
- Segmented-unsegmented
- Positive stranded-Negative stranded

2. Capsid

- Icosahedral Symmetry
- Helical Symmetry
- Complex Symmetry

Classification of Viruses

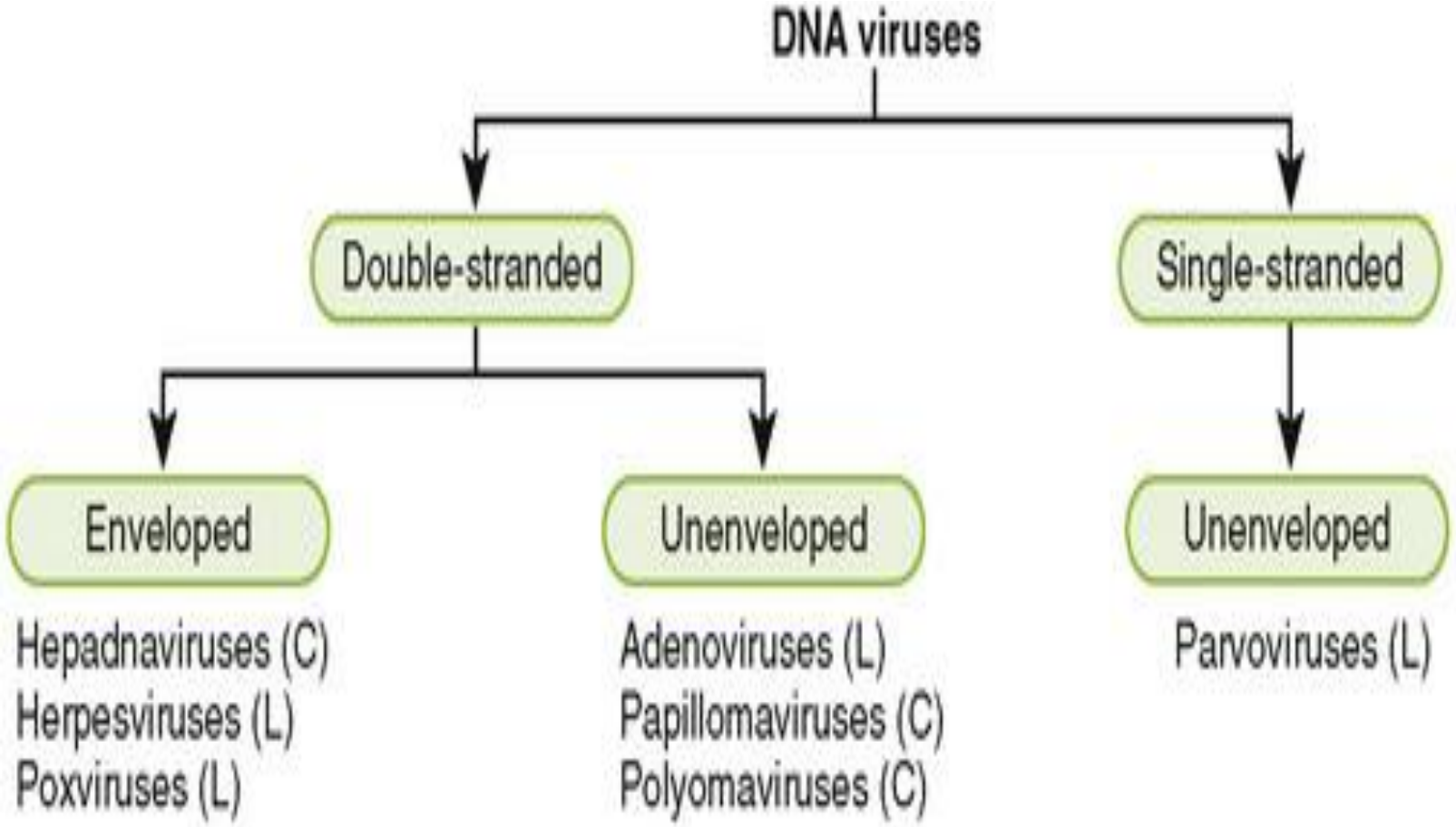
3. Viral Envelope

- Non-enveloped
- Enveloped

4. Size

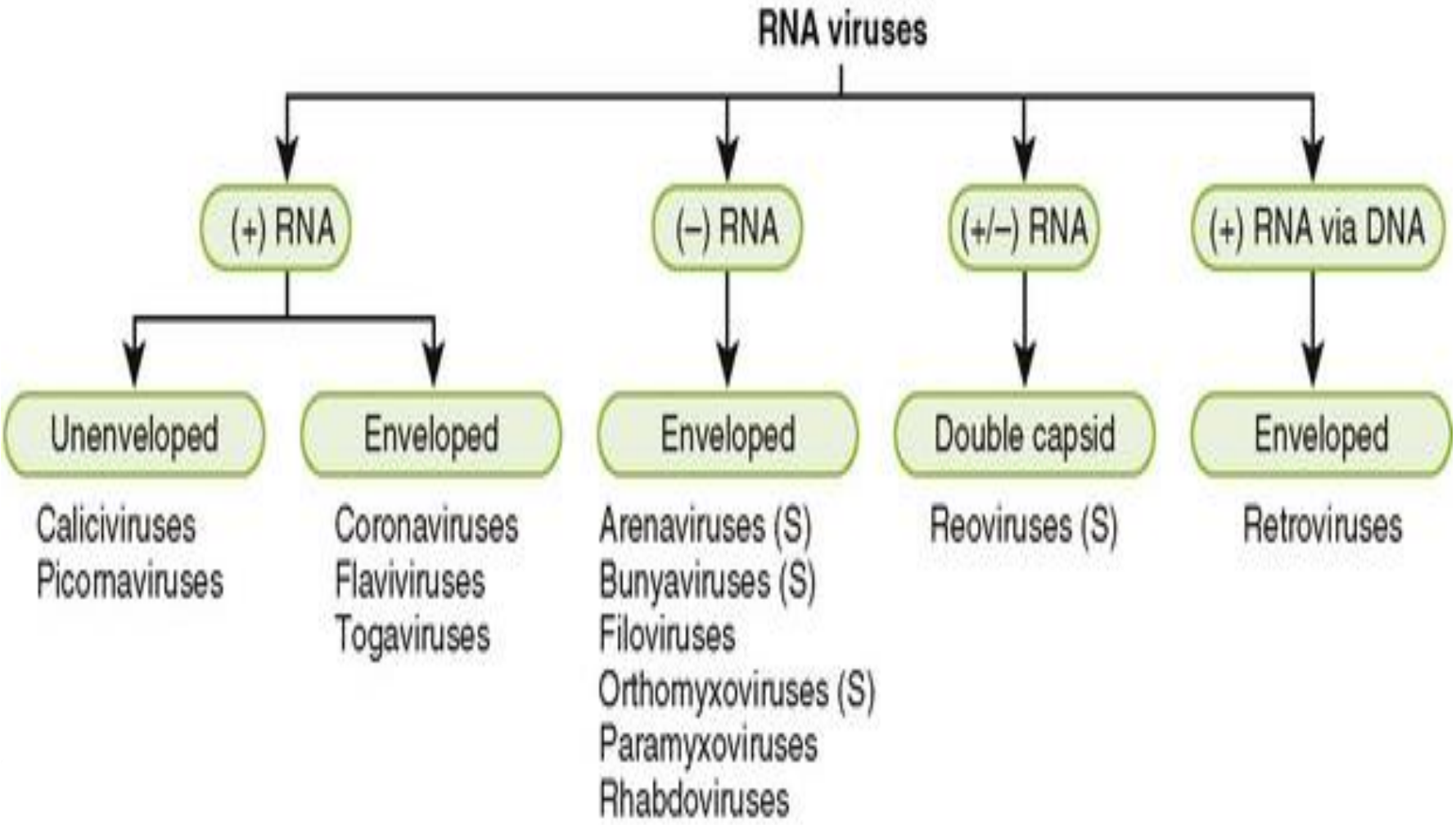
- Diameter of the capsid (viruses with helical symmetry)
- Number of capsomeres in icosahedral viruses

Classification of Viruses



- Parvoviruses have a linear single-stranded DNA genome
- Complex symmetry found in Poxviruses

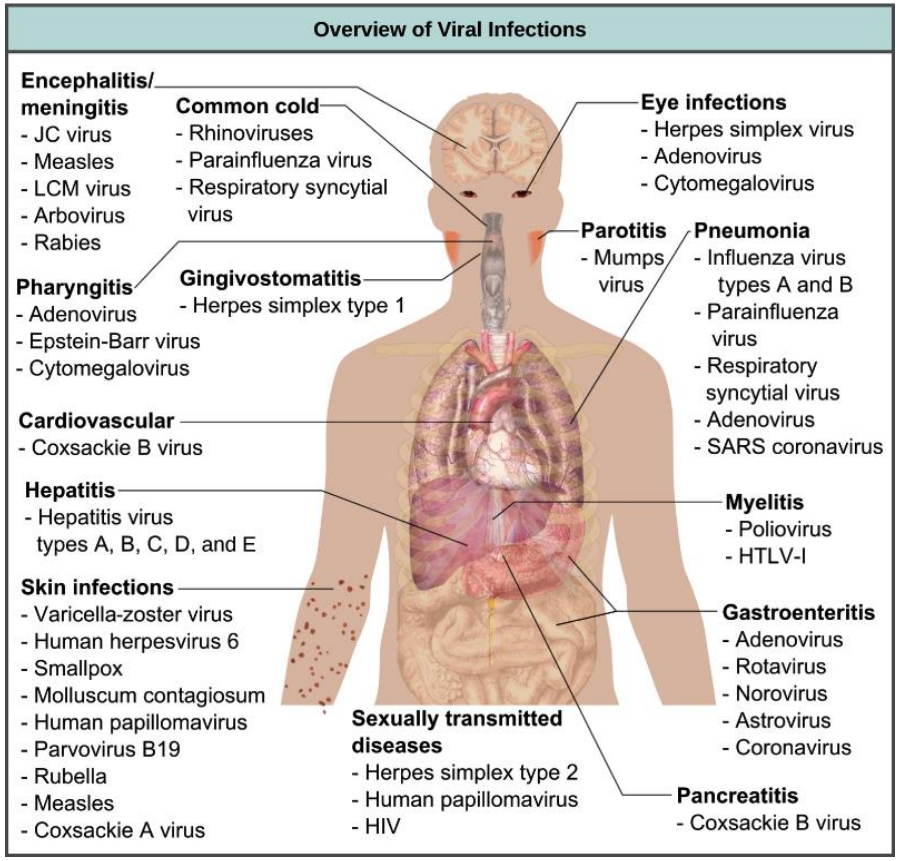
Classification of Viruses



Reoviruses contain double-stranded RNA

Classification of Viruses

Viruses in particular often have an affinity for a specific tissue or organ. For example, Rabies and Polio viruses attack the nervous system, Hepatitis A and Hepatitis B attack liver.



https://www.khanacademy.org/science/biology/biology-of-viruses/virus-biology/a/animal-viruses-hiv

Classification of Viruses

Viruses That Cause Systemic Infections

- Viruses causing this type of infection spread over the whole body through blood circulation.

- Result of this, they affect many tissues and organs.

- Their clinical findings are mostly fever, fatigue, skin rash etc. For example; Smallpox, Measles, Rubeola, Varicella zoster

Classification of Viruses

Viruses That Invade Specific Organs

- Some viruses that invade only certain organs and tissues cause infections by spreading through blood circulation, peripheral nerves or other ways.

- Viruses generally invade the following body systems.

Classification of Viruses

Nervous System Diseases

Viruses entering organism cause diseases with the symptoms of paralysis, meningitis, encephalitis by infecting nervous system cells. For example; Poliomyelitis, Rabies.

Respiratory System Diseases

Some viruses enter the body through respiratory droplets and settle in respiratory system cells, cause diseases.

For example; Influenza, Parainfluenza, pneumonia due to Respiratory Syncytial Virus, New Coronavirus (COVID-2019).

Classification of Viruses

Localized Diseases of Skin and Mucosal Membranes

Some viruses cause diseases by settling in the skin and mucosal membranes. For example; Herpes simplex, Molluscum contagiosum.

Eye Diseases

Some viruses cause diseases by settling in the eye. For example; Viral conjunctivitis caused by Adenovirus or Herpes simplex.

Classification of Viruses

Liver Diseases

Viruses that cause liver diseases settle in the liver through blood circulation or directly, although this type of disease can also be seen as a result of a complication of systemic infections. For example; Hepatitis A and Hepatitis B.

Salivary Glands Diseases

Viruses that have affinity to salivary glands cause these types of diseases. For example; infections caused by Mumps and Cytomegalovirus.

Classification of Viruses

Diseases of the Digestive System

Viruses that have affinity to digestive system cause these types of diseases. They enter body orally. For example; gastroenteritis caused by Enteroviruses.

Veneral Diseases

Viruses that are found in genital secretions cause infections through sexual intercourse. For example; Herpes simplex, Hepatitis B, Papillomavirus, Molluscum contagiosum, HIV.

ENVELOPED DNA VIRUSES

Herpesvirus

Herpes virus contain six major pathogens:

- ✓ **Herpes Simplex Virus Type 1**
- ✓ **Herpes Simplex Virus Type 2**
- ✓ **Varicella zoster Virus**
- ✓ **Cytomegalovirus**
- ✓ **Epstein-Barr Virus**
- ✓ **Human Herpesvirus 8**

ENVELOPED DNA VIRUSES

Herpesvirus

- Herpes viruses are significant as they cause latent infections.

- In these type of infections, acute infection is followed by latent infection.

- Latent infection reactivate in case of contraction with an activating agent or immunosuppression.

ENVELOPED DNA VIRUSES

Herpesvirus

- Herpes Simplex Virus Type 1, Herpes Simplex Virus Type 2 and Varicella zoster cause vesicular rash both in acute infection and after reactivation.

- In general acute infections are more severe than reactivated infections.

- Cytomegalovirus and Epstein-Barr Virus don’t cause vesicular rash .

ENVELOPED DNA VIRUSES
Herpes Simplex Virus Type 1

Diseases: Herpes labialis (herpes), keratitis, encephalitis

Transmission: Spread by contact, as the virus is shed in saliva, tears and other secretions

Pathogenesis: Initial vesicular lesions are seen in the mouth or face. Then the virus travel along the axon to the ganglia where the infection becomes latent. Sunlight, fever, stress are the risk factors for the reactivation. Life-threatening internal organs spread can be seen in patients with suppressed cell-mediated immunity.

ENVELOPED DNA VIRUSES

Herpes Simplex Virus Type 1

Laboratory diagnosis: The virus causes cytopathic effect in cell culture. It is identified with antibody neutralization and fluorescent antibody tests.

Treatment: Acyclovir is used to treat the overwhelming majority of cases of HSV-1. Acyclovir is effective only against actively replicating viruses; it does not cure the latent herpesvirus. Trifluorothymidine is used to treat keratitis.

ENVELOPED DNA VIRUSES

Herpes Simplex Virus Type 1

Prevention: Treatment with zinc oxide or zinc sulfate containing cream, an anesthetic cream, or an antiviral cream has a favorable effect on the duration of symptoms, if applied promptly. If antiviral medicine (topical or oral) is started before exposure to the triggering factor (sunlight), it will provide some protection.

There is no approved vaccine against Herpes simplex.

ENVELOPED DNA VIRUSES

Herpes Simplex Virus Type 2

Diseases: Herpes genitalis, aseptic meningitis, neonatal HSV infections.

Transmission: HSV-2 is mainly transmitted during sex, through contact with genital surfaces, skin, sores or fluids of someone infected with the virus. In rare circumstances, HSV-2 infection can be transmitted from a mother to her infant during birth.

ENVELOPED DNA VIRUSES

Herpes Simplex Virus Type 2

Pathogenesis: Initial vesicular lesions are seen in the genital organs. Then the virus travels along the axon to the ganglia where the infection becomes latent. In general acute infections are more severe than reactivated infections.

Neonatal HSV-2 infections may be life threatening in newborns due to reduced cellular immunity.

Laboratory Diagnosis: The virus causes cytopathic effect in cell culture. It is identified with antibody neutralization and fluorescent antibody tests.

ENVELOPED DNA VIRUSES

Herpes Simplex Virus Type 2

Treatment: Acyclovir is used to treat the overwhelming majority of cases of HSV-2. Acyclovir is effective only against actively replicating viruses; it does not cure the latent Herpesvirus.

Prevention: Individuals with HSV-2 should avoid any type of sexual activity with other people during an outbreak.

ENVELOPED DNA VIRUSES

Herpes Simplex Virus Type 2

Prevention: If the individual is not experiencing symptoms but has been diagnosed with the virus, a condom should be used during intercourse. But even when using a condom, the virus can still be passed to a partner from uncovered skin. Women who are pregnant and infected may have to take medicine to prevent the virus from infecting their unborn babies.

There is no approved vaccine against Herpes simplex.

ENVELOPED DNA VIRUSES

Varicella Zoster Virus

Diseases: Varicella (Chickenpox) and Herpes Zoster (Shingles). Shingles, also called Herpes zoster or Zoster, is a painful skin rash caused by the Varicella zoster virus. Primary VZV infection leads to varicella, VZV can reactivate at a later time, causing Herpes zoster .

Transmission: Transmitted person to person by direct contact, inhalation of aerosols from vesicular fluid of skin lesions of acute Varicella or Zoster, or aerosolized respiratory tract secretions. Shingles is not a contagious disease.

ENVELOPED DNA VIRUSES

Varicella Zoster Virus

Pathogenesis: Infection initiates in oropharynx. It spreads to organs like liver and then skin through blood circulation. After the acute infection, viruses settle in sensory ganglion neurons and remain latent. VZV can reactivate at a later time causing Herpes zoster, especially in immunocompromised elderly patients.

Laboratory diagnosis: The virus causes cytopathic effect in cell culture. It is identified with antibody neutralization and fluorescent antibody tests.

ENVELOPED DNA VIRUSES

Varicella Zoster Virus

Treatment: The treatment of Herpes zoster has three major objectives:

(1) treatment of the acute viral infection

(2) treatment of the acute pain associated with Herpes zoster

(3) prevention of postherpetic neuralgia

Antiviral agents, oral corticosteroids and adjunctive individualized pain-management modalities are used to achieve these objectives.

ENVELOPED DNA VIRUSES

Varicella Zoster Virus

Prevention: There are two Chickenpox vaccines approved for use in the United States, one of which is combined with vaccines for other diseases:

Varivax: The Food and Drug Administration (FDA) approved this vaccine in 1995 for use in people 1 year of age and older.

ProQuad: FDA approved this vaccine in 2005 for use in children ages 1 through 12 years of age. It protects against measles, mumps, rubella, and varicella (MMRV).

ENVELOPED DNA VIRUSES
Varicella Zoster Virus

Prevention: In our country live, attenuated vaccine is used single dose in twelve-month-old children. Pregnancy should be avoided for one month following the vaccination. It is not administered to infants under twelve months. It is not life-time protective. Readministration may be needed.

Zoster vaccine is recommended for everyone over age 60. Because Herpes zoster is more life threatening in elderly than young. The immunocompromised should be administered acyclovir and Varicella zoster immunoglobulin to prevent the spread of virus.

ENVELOPED DNA VIRUSES
Cytomegalovirus (CMV)

- Cytomegalovirus is a common virus that infects people of all ages. In the United States, nearly one in three children are already infected with CMV by age 5 years. Over half of adults by age 40 have been infected with CMV. Once CMV is in a person's body, it stays there for life and can reactivate.
- Most people infected with CMV show no signs or symptoms. That’s because a healthy person's immune system usually keeps the virus from causing illness.

ENVELOPED DNA VIRUSES

Cytomegalovirus (CMV)

- However, CMV infection can cause serious health problems for people with weakened immune systems, as well as babies infected with the virus before they are born.

- Most people with CMV infection have no symptoms and aren’t aware that they have been infected. In some cases, infection in healthy people can cause mild illness that may include; fever, sore throat, fatigue and swollen glands. Occasionally, CMV can cause mononucleosis or hepatitis (liver problem).

ENVELOPED DNA VIRUSES

Cytomegalovirus (CMV)

- People with weakened immune systems who get CMV can have more serious symptoms affecting the eyes, lungs, liver, esophagus, stomach, and intestines.

- Babies born with CMV can have brain, liver, spleen, lung, and growth problems. Hearing loss is the most common health problem in babies born with congenital CMV infection, which may be detected soon after birth or may develop later in childhood.

ENVELOPED DNA VIRUSES
Cytomegalovirus (CMV)

Transmission: People with CMV may shed (pass) the virus in body fluids, such as urine, saliva, blood, tears, semen, and breast milk. CMV is spread from an infected person in the following ways: -from direct contact with urine or saliva, especially from babies and young children -through sexual contact -from breast milk -through transplanted organs and blood transfusions –from mother to child during pregnancy (congenital CMV).

Laboratory Diagnosis: Blood tests can be used to diagnose CMV infections in people who have symptoms.

ENVELOPED DNA VIRUSES

Cytomegalovirus (CMV)

Treatment: Healthy people who are infected with CMV usually do not require medical treatment. Medications are available to treat CMV infection in people who have weakened immune systems and babies who show symptoms of congenital CMV infection. Ganciclovir is an antiviral medication used to treat CMV infections.

Prevention: There is no approved vaccine against CMV.

ENVELOPED DNA VIRUSES

Epstein-Barr Virus (EBV)

- Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a member of the herpes virus family.
- It is one of the most common human viruses. EBV is found all over the world. Most people get infected with EBV at some point in their lives.
- EBV spreads most commonly through bodily fluids, primarily saliva.
- EBV can cause **infectious mononucleosis.**

ENVELOPED DNA VIRUSES

Epstein-Barr Virus (EBV)

Symptoms of EBV infection can include; fatigue, fever, inflamed throat, swollen lymph nodes in the neck, enlarged spleen, swollen liver, rash.

Many people become infected with EBV in childhood. EBV infections in children usually do not cause symptoms, or the symptoms are not distinguishable from other mild, brief childhood illnesses.

ENVELOPED DNA VIRUSES

Epstein-Barr Virus (EBV)

- People who get symptoms from EBV infection, usually teenagers or adults, get better in two to four weeks. However, some people may feel fatigued for several weeks or even months.
- After you get an EBV infection, the virus becomes latent in your body. In some cases, the virus may reactivate. This does not always cause symptoms, but people with weakened immune systems are more likely to develop symptoms if EBV reactivates.

ENVELOPED DNA VIRUSES

Epstein-Barr Virus (EBV)

- EBV spreads most commonly through bodily fluids, especially saliva. However, EBV can also spread through blood and semen during sexual contact, blood transfusions, and organ transplantations.

- EBV can be spread by using objects, such as a toothbrush or drinking glass, that an infected person recently used. The virus probably survives on an object at least as long as the object remains moist.

ENVELOPED DNA VIRUSES

Epstein-Barr Virus (EBV)

- The first time you get infected with EBV (primary EBV infection) you can spread the virus for weeks and even before you have symptoms.
- Once the virus is in your body, it stays there in a latent state. If the virus reactivates, you can potentially spread EBV to others no matter how much time has passed since the initial infection.
- EBV infection can be confirmed with a blood test that detects antibodies.

ENVELOPED DNA VIRUSES

Epstein-Barr Virus (EBV)

- There is no vaccine to protect against EBV infection.

- You can help protect yourself by not kissing or sharing drinks, food, or personal items, like toothbrushes, with people who have EBV infection.

- There is no specific treatment for EBV. However, some things can be done to help relieve symptoms, including; drinking fluids to stay hydrated, getting plenty of rest, taking medications for pain and fever.

NON-ENVELOPED DNA VIRUSES

Human Papillomavirus (HPV)

Genital warts. HPV can cause cervical and other cancers including cancer of the vulva, vagina, penis, or anus.

Transmission: Direct contact with skin or genital lesions (by having vaginal, anal, or oral sex with someone who has the virus)

Common high–risk types that cause cancer: HPV-16 & HPV-18.

- HPV-16 is the most common high-risk type, it is found in almost half of all cervical cancers.
- HPV-18 is also a common high-risk virus – it accounts for 10% to 12% of cervical cancers.

NON-ENVELOPED DNA VIRUSES
Human Papillomavirus (HPV)

- It is recommended that the HPV vaccine can be given to 11 to 12 years old girls, but it can be given to girls as young as 9 years old.
- The vaccine should be given before the onset of sexual activity.
- Gardasil protects against four HPV types (6,11,16,18) which cause 70% of cervical cancer and 90% of genital warts.
- Condoms have been shown to lower the risk of HPV.

NON-ENVELOPED DNA VIRUSES

Parvovirus B19

- Parvoviruses are non-enveloped, single-stranded DNA viruses
- Parvovirus B19 most commonly causes fifth disease, a mild rash illness that usually affects children. Adults can get infected with Parvovirus B19, too.
- Parvovirus B19 spreads through respiratory secretions, such as saliva, sputum, or nasal mucus, when an infected person coughs or sneezes. Parvovirus B19 can also spread through blood or blood products. A pregnant woman who is infected with Parvovirus B19 can pass the virus to her baby.