Introduction to Microbiology for M.D. Students

Introduction to Medical Virology

University of Jordan

School of Medicine

Department of Pathology, Microbiology and Forensic Medicine

Section of Microbiology and Immunology

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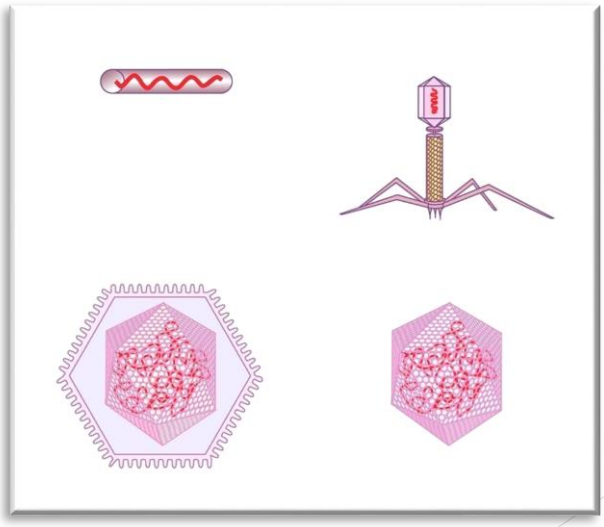
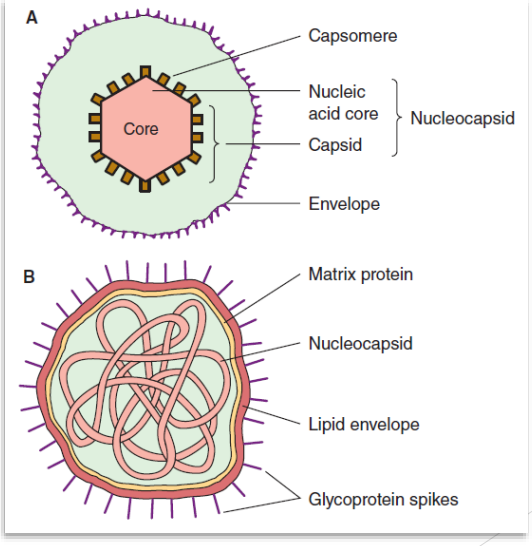
What are viruses?



General Characteristics of Viruses

- Obligate intracellular parasites.
- Extremely small size.
- Genome is either DNA or RNA (never both).
- Extremely variable.
- Uncertain origin.

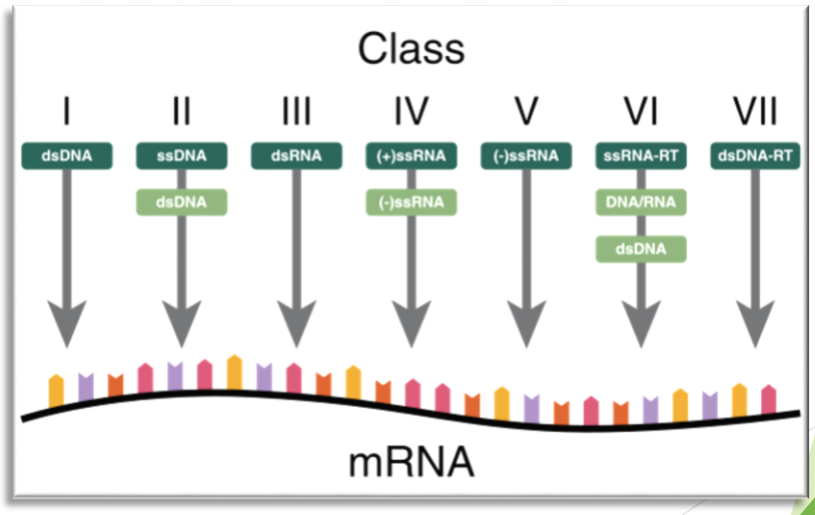
Terminology



Virus Taxonomy-ICTV Classification

- Order *(-virales)*
- Family *(-viridae)*
- Subfamily *(-virinae)*
- Genus *(-virus)*
- Species

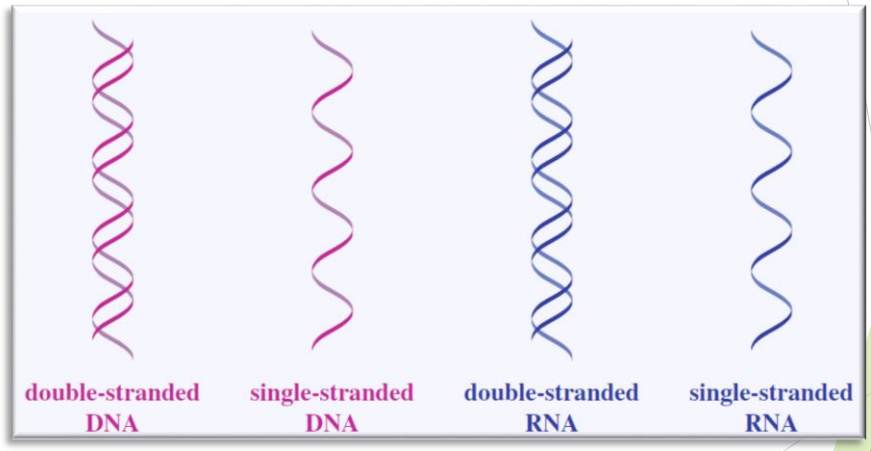
Baltimore Classification



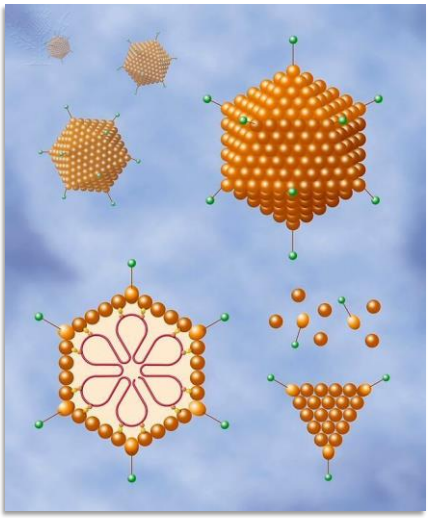
Virus Classification

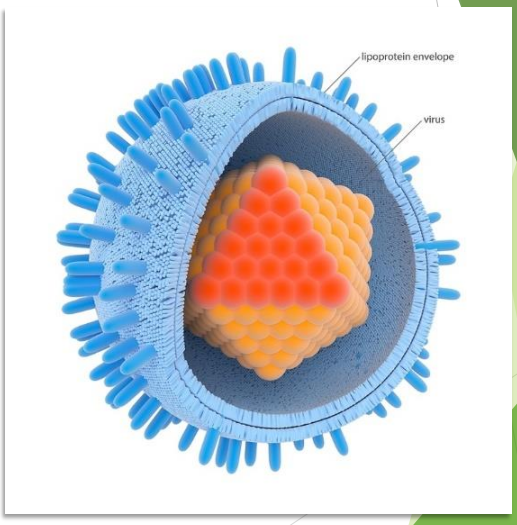
- **Morphology** (capsid symmetry, presence of an envelope, etc.).
- **Host organism** (human, animal, plant, bacteria).
- **Type of disease** (hepatitis viruses, respiratory viruses, etc.).

Virus Classification



Virus Classification





Overview of Human Viruses-DNA Viruses

- HHAPPPy viruses:

✓ ***Herpesviridae***

✓ ***Hepadnaviridae***

✓ *Adenoviridae*

✓ *Papovaviridae*

✓ *Parvoviridae*

✓ ***Poxviridae***

- Replicate in the nucleus (except Pox).
- Double-stranded (except Parvo).
- Naked vs. **Enveloped.**

Overview of Human Viruses-RNA Viruses

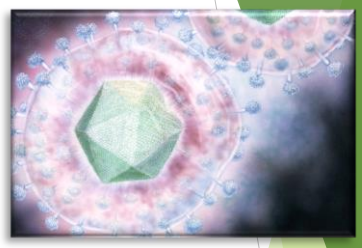
- ✓ *Arenaviridae*
- ✓ *Bunyaviridae*
- ✓ *Caliciviridae*
- ✓ *Coronaviridae*
- ✓ *Filoviridae*
- ✓ *Orthomyxoviridae*
- ✓ *Picornaviridae*
- ✓ *Reoviridae*
- ✓ *Retroviridae*
- ✓ *Rhabdoviridae*
- ✓ *Togaviridae*
- ✓ *Paramyxoviridae*

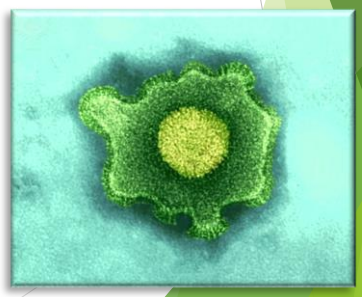
Herpesviruses: An Overview

- The outstanding property of herpesviruses is their ability to establish **lifelong persistent infections** in their hosts and to undergo **periodic reactivation**.
- Their frequent reactivation in immunosuppressed patients causes serious health complications.

Herpesviruses: An Overview

- Double-stranded DNA virus.
- Icosahedral symmetry.
- Enveloped.
- Envelope is acquired from the **nuclear membrane**.
- Baltimore Class I.





Herpes Simplex Viruses-Introduction

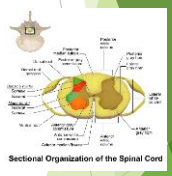
- Hippocrates used the Greek word herpes to describe lesions that seem to creep or crawl along the skin.
- ICTV designate the two species as human herpesviruses 1 and 2 (HHV-1) and (HHV-2).
- The two species were first identified as two distinct serotypes; herpes simplex viruses 1 and 2 (**HSV-1**) and (**HSV-2**).

Herpes Simplex Viruses Taxonomy

- Order *(Herpesvirales)*
  - Family *(Herpesviridae)*
    - Subfamily *(Alphaherpesvirinae)*
      - Genus *(Simplexvirus)*
        - Species *(Human herpesvirus 1; HHV-1)*
        - Species *(Human herpesvirus 2; HHV-2)*

Herpes Simplex Viruses-Important Features

- *Natural Host:* Human, mammals.
- *Tropism:* Epithelial mucosal cells.



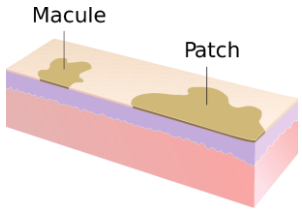
- *Latency:* Sensory neurons (dorsal ganglia).
- *Cellular receptors:* Heparan sulfate among others.

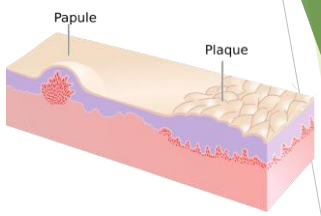
- *Geography:* Worldwide.

Herpes Simplex Viruses-Important Features

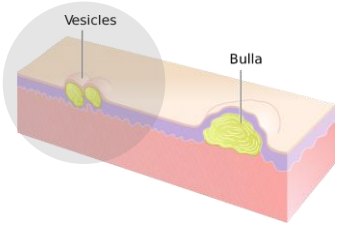
- Transmission (HHV-1): Direct contact, saliva.
- Transmission (HHV-2): Sexual contact, vertical.
- HSV is transmitted by contact with an individual excreting virus.
- The virus must encounter mucosal surfaces or broken skin in order for an infection to be initiated (unbroken skin is resistant).

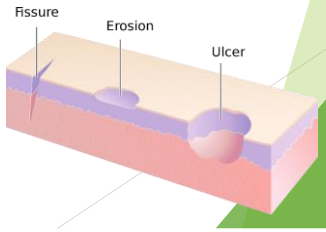
Herpes Simplex Viruses-Characteristic Lesions





Vesicles are circumscribed epidermal elevations containing clear fluid and less than 1 cm in diameter. If the lesion has a diameter of greater than 1 cm, it is called a **bulla**. Vesicles and bullae are commonly called **blisters**.



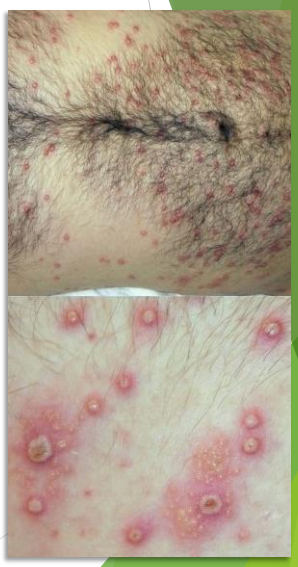


Herpes Simplex Viruses-Pathogenesis & Pathology

- **Primary infection**
  - Viral replication occurs first at the site of infection.
  - HSV then invades local nerve endings and is transported by retrograde axonal flow to dorsal root ganglia.
  - After further replication, latency is established.
  - Oropharyngeal infections result in latent infections in the **trigeminal ganglia**.
  - Genital infections lead to latently infected **sacral ganglia**.

Herpes Simplex Viruses-Pathogenesis & Pathology

- **Primary infection**
  - Primary HSV infections are usually asymptomatic.
  - Most symptomatic primary infections are mild.
  - Only rarely does systemic disease develop.
  - Widespread organ involvement can result when an immunocompromised host is not able to limit viral replication and viremia ensues.



Herpes Simplex Viruses-Pathogenesis & Pathology

- **Latent infection**
  - Virus resides in latently infected ganglia with very few viral genes being expressed.

Herpes Simplex Viruses-Pathogenesis & Pathology

- **Latent infection**
  - Provocative stimuli can reactivate virus from the latent state, including:

✓ Axonal injury.

✓ Fever.

✓ Physical or emotional stress.

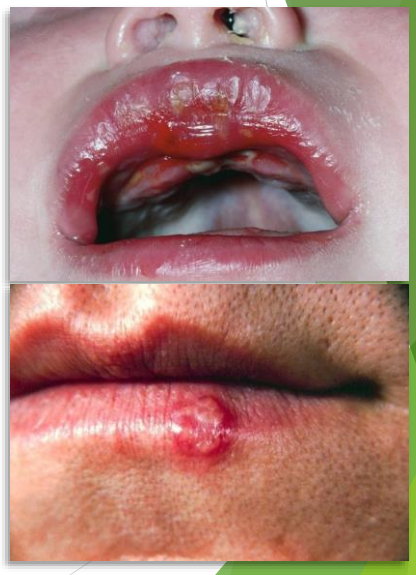
✓ Exposure to ultraviolet light.

Herpes Simplex Viruses-Pathogenesis & Pathology

- **Latent infection**
  - The virus follows axons back to the peripheral site, and replication proceeds at the skin or mucous membranes.
  - HSV-specific immunity limits local viral replication, so that recurrent infections are less extensive and less severe.
  - Many recurrences are **asymptomatic**, reflected only by viral shedding in secretions.

Primary/Recurrent Oropharyngeal Disease

- **Gingivostomatitis.**
- **Pharyngitis.**
- **Mononucleosis-like syndrome.**
- **Herpes labialis (cold sores).**



Primary/Recurrent Oropharyngeal Disease

- The incubation period ranges from 2-12 days, with a mean of 4 days.
- The duration of clinical illness may be from 2-3 weeks.

Primary/Recurrent Genital Disease

- **Genital herpes:**
  - Symptomatic primary genital infection is the most severe, lasting about 3 weeks.

Primary/Recurrent Genital Disease

- **Genital herpes**
  - In females: Excruciatingly painful lesions in the vulva, perineum, buttocks, cervix, and/or vagina associated with inguinal adenopathy and dysuria.
  - In males: Lesions involving the glans penis or the penile shaft with extragenital lesions of the thigh, buttocks, and perineum.
  - Proctitis can occur in male homosexuals.
  - Recurrences of genital herpetic infections are common and tend to be mild.

Primary/Recurrent Genital Disease

- **Genital herpes**
  - Recent evidence documented the increase in the frequency of genital (HSV-1) compared with genital (HSV-2) infection. This trend has been seen both in Europe, Australia and in the US.
  - Oral shedding of HSV-2 is infrequent.

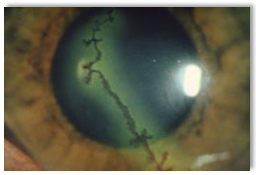
Neonatal Herpes Simplex Virus Infection

- The estimated incidence of neonatal HSV infection is 1 in 3,000 to 1 in 5,000 deliveries per year.
- May be acquired in utero, during birth, or after birth.
- Neonatal herpes infections are almost always symptomatic.
- The overall mortality rate of untreated disease is 50%.
- Many survivors of severe infections are left with permanent neurologic impairment.

Toxoplasma
others
Rubella
CMV
Herpes

Herpes Simplex Keratoconjunctivitis

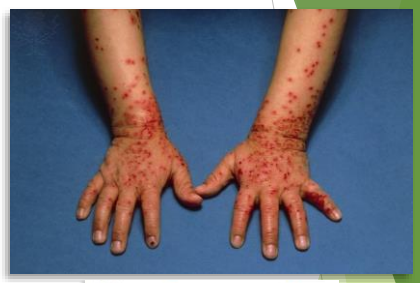
- ✓ HHV-1 infections may occur in the eye, producing severe keratoconjunctivitis.
- ✓ Recurrent lesions of the eye are common and appear as dendritic keratitis or corneal ulcers or as vesicles on the eyelids.
- ✓ Keratitis may end up in blindness.



Pathognomonic Dendritic Ulceration

Herpetic Skin Infections

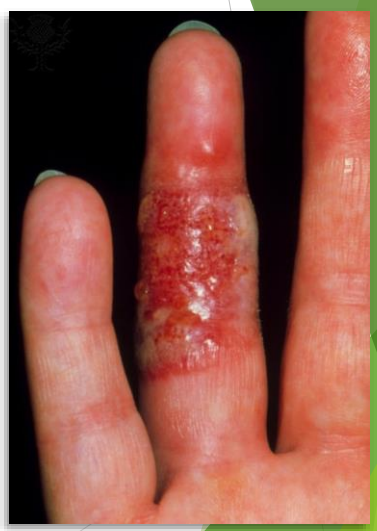
- Usually manifest as **eczema herpeticum** in patients with underlying atopic dermatitis.



- Disseminated HSV infections have been also reported among wrestlers (**herpes gladiatorum**).

Herpetic Skin Infections

- Rarely, the infection may be spread to the distal phalanx via direct inoculation and cause pain, swelling, erythema, and vesicles in an entity known as **herpetic whitlow**.



Infections of the Immunocompromised Host

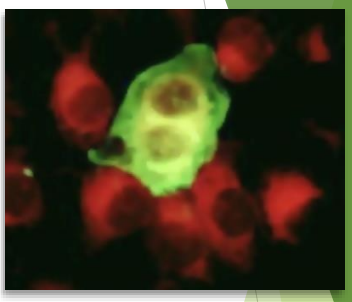
- Immunocompromised patients are at increased risk of developing **severe HSV infections**.
- These include patients immunosuppressed by disease or therapy.
- Patients with deficient cellular immunity suffer more frequent and more severe HSV infections.
- Herpes lesions may spread and involve the respiratory tract, esophagus, and intestinal mucosa.
- In most cases, the disease reflects **reactivation of latent HSV infection**.

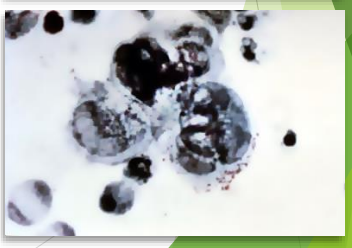
Infections of the Central Nervous System

- HSV encephalitis is one of the most devastating of all HSV infection.
- **HSV-1 (HHV-1) is considered the most common cause of sporadic, fatal encephalitis**.
- **The disease carries a high mortality rate**.
- Aseptic meningitis is a common occurrence in individuals with primary genital HSV infections.

Diagnosis

- **Clinical diagnosis**.
- Virus isolation is a definitive diagnostic method (samples include: skin scrapings, throat swab, CSF).
- PCR detection of viral DNA.
- Cytopathology with Giemsa stain of scrapings (**Tzanck smear**).
- Serology.





Treatment

- Nucleoside analogues: acyclovir, valacyclovir, penciclovir and famciclovir.
- All nucleoside and nucleotide analogues must be activated by phosphorylation usually to the triphosphate form to exert their action.
- Mechanism of action: Inhibition of viral genome replication through inhibiting the viral polymerase.

Treatment

- The virus thymidine kinase is much more potent compared to the cellular kinases in activating the drug, ∴ it is more efficient in virus-infected cells.
- Treatment is important in herpes encephalitis, neonatal herpes, and disseminated infections in immunocompromised patients.
- Despite treatment, HSV remains latent in sensory ganglia.
- Drug-resistant virus strains may emerge.

Epidemiology

- ✓ In 2012, an estimated 3.7 billion people under the age of 50, or 67% of the world population, had HSV-1 infection (WHO).
- ✓ The overall prevalence of HSV-2 among 15–49 year olds world-wide in 2012 is estimated to be 11% (over 400 million people).

Prevention and Control

- Educational efforts must be developed for adolescents and those at greatest risk.
- Surgical abdominal delivery.
- Hospital staff: Temporary removal of personnel who have cold sores is advocated for clinical services.
- Experimental vaccines.

Varicella Zoster Virus (VZV)-Introduction

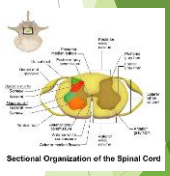
- Zoster was derived from a Greek word meaning belt.
- Shingles was derived from a Latin word meaning belt.
- **The virus is highly contagious**.

Varicella Zoster Virus-Taxonomy

- Order (*Herpesvirales*)
  - Family (*Herpesviridae*)
    - Subfamily (*Alphaherpesvirinae*)
      - Genus (*Varicellovirus*)
        - Species (*Human herpesvirus 3; HHV-3*)

Varicella Zoster Virus-Important Features

- *Natural Host:* Human.
- *Tropism:* Epithelial mucosal cells.
- *Latency:* **Sensory neurons (dorsal ganglia)**.

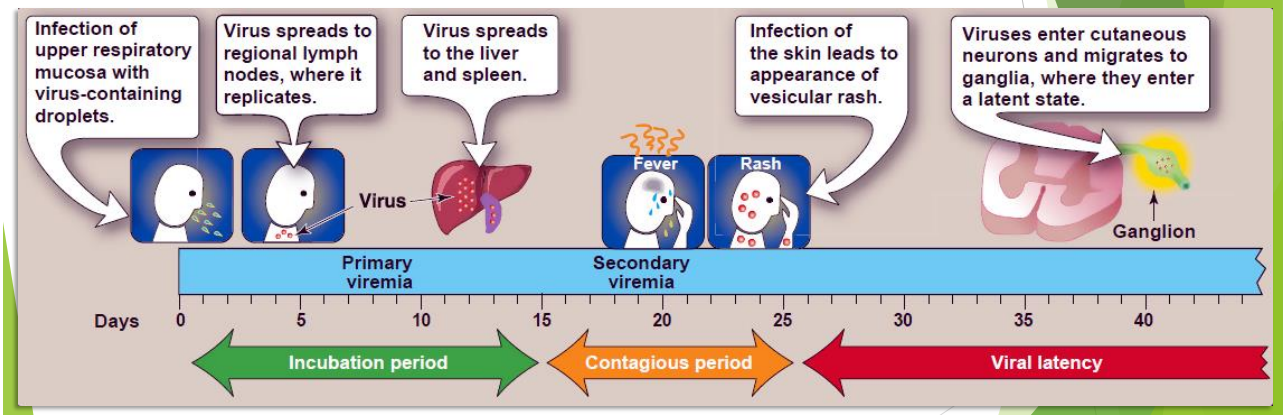


- *Cellular receptors:* Heparan sulfate among others.
- *Geography:* Worldwide.

Varicella Zoster Virus-Important Features

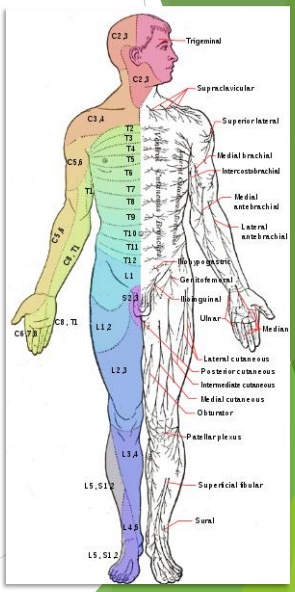
- Transmission (HHV-3): Respiratory, contact.
- Varicella (chickenpox) is highly communicable and is a common epidemic disease of childhood (most cases occur in children under 10 years of age).
- Zoster occurs sporadically, chiefly in adults and without seasonal prevalence. Ten to 20 percent of adults will experience at least one zoster attack during their lifetime, usually after the age of 50.

VZV-Pathogenesis & Pathology



VZV-Pathogenesis & Pathology

- The skin lesions of zoster are histopathologically identical to those of varicella.
- Often only a single ganglion may be involved.
- As a rule, **the distribution of lesions in the skin corresponds closely to the areas of innervation from an individual dorsal root ganglion**.



Varicella (Chickenpox)

- **Subclinical varicella is unusual**.
- The incubation period: 10–21 days.
- Malaise and fever are prodromal, followed by rash, first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa.
- Successive fresh vesicles appear in crops, so all stages of macules, papules, vesicles, and crusts may be seen at one time.
- The rash lasts about 5 days.
- Complications are rare in normal children, and the mortality rate is very low.

Zoster (Shingles)

- **Zoster occurs in immunocompromised persons**.
- It starts with severe pain in the area of skin or mucosa supplied by the sensory nerves and ganglia.
- Within a few days, a crop of vesicles appears over the skin supplied by the affected nerves.
- The trunk, head, and neck are most commonly affected.
- **The most common complication of zoster in the elderly is postherpetic neuralgia which is a protracted pain that may continue for months**.

Diagnosis

- Clinical.
- Tzanck smear.
- Serology.
- PCR (polymerase chain reaction).

Treatment

- **Varicella in normal children is a mild disease and requires no treatment.**
- Varicella-zoster immune globulin can be used to prevent the development of the illness.
- Several antiviral compounds provide effective therapy for varicella, including acyclovir, valacyclovir and famciclovir.
- Acyclovir can prevent the development of systemic disease in varicella-infected immunosuppressed patients and can halt the progression of zoster in adults.
- **Acyclovir does not appear to prevent postherpetic neuralgia.**

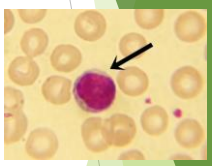
Prevention & Control

- A live attenuated varicella vaccine is highly effective at inducing protection from varicella.

Kaposi's Sarcoma-Associated Herpesvirus (KSHV)-Taxonomy

- Order *(Herpesvirales)*
  - Family *(Herpesviridae)*
    - Subfamily *(Gammaherpesvirinae)*
      - Genus *(Rhadinovirus)*
        - Species *(Human herpesvirus 8; HHV-8)*

Kaposi's Sarcoma-Associated Herpesvirus-Important Features



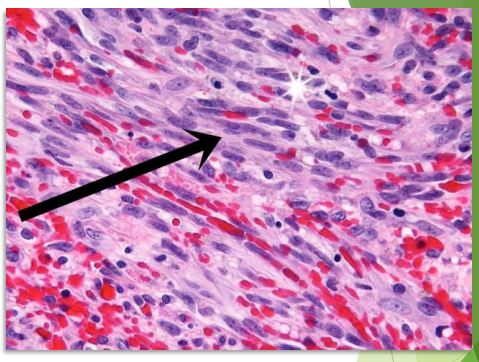
- Natural Host: *Human.*
- Tropism: ***B lymphocytes.***
- Latency: ***B lymphocytes.***
- Cellular receptors: *Heparan sulfate, integrins, others*
- Geography: *Africa, Mediterranean and Eastern EU. Worldwide linked to HIV infection.*

Kaposi's Sarcoma-Associated Herpesvirus-Important Features

- Transmission (HHV-8): Sexual contact, saliva
- Some infections are acquired early in life by nonsexual routes, possibly through contact with oral secretions.
- It appears to be sexually transmitted among gay men, who have a higher seroprevalence compared to the general population.

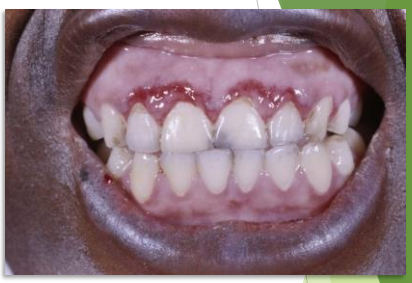
Kaposi's Sarcoma-Associated Herpesvirus-Important Features

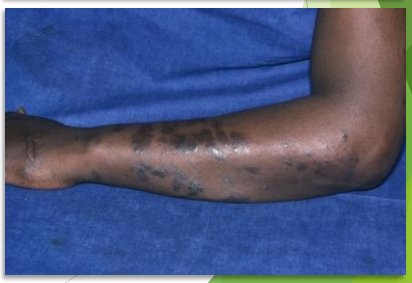
- Kaposi's sarcoma (KS) seems to originate from the viral modified pluripotent mesenchymal cells of the connective tissue transformed in **spindle-shaped KS cells**, followed by a mesenchymal-endothelial transition.



Kaposi's Sarcoma (KS)

- Nodular lesions of variable colors affecting the skin, mouth, GI tract or respiratory tract.
- Four classes of KS including:
  1. Classic KS.
  2. Endemic or African KS.
  3. Iatrogenic KS associated with immunosuppressive therapies in transplant patients.
  4. **Epidemic or AIDS-related KS.**





Clinical conditions associated with KSHV

- KS has variable clinical presentation (limited to fulminant, indolent to aggressive).
- Primary effusion lymphoma (PEL).
- Multicentric Castleman's disease (MCD).

Epidemiology, Diagnosis and Treatment

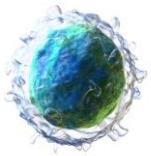
- KS incidence is 1 in 100,000 in the general population, whereas in HIV-infected individuals, the incidence is around 1 in 20.
- Dx: Diagnosis of KS is done through **histopathology**.
- Confirmation of dx is done by immunohistochemistry in tissues using monoclonal antibodies to the KSHV.
- Treatment: Highly active antiretroviral therapy (HAART) can induce AIDS-KS regression. Isolated lesions are treated with radiotherapy. Systemic chemotherapy is useful for the treatment of disseminated disease.

Epstein–Barr virus (EBV)-Taxonomy

- Order (*Herpesvirales*)
  - Family (*Herpesviridae*)
    - Subfamily (*Gammaherpesvirinae*)
      - Genus (*Lymphocryptovirus*)
        - Species (***Human herpesvirus 4***; *HHV-4*)

EBV-Important Features

- ❖ *Natural Host:* *Human, mammals.*
- ❖ *Tropism:* ***B cells, oral epithelial cells.***
- ❖ *Latency:* ***B cells.***
- ❖ *Cellular receptors:* ***Complement Receptor 2 CR2 (CD21).***
- ❖ *Geography:* *Worldwide.*



Lymphocyte
B cell

EBV-Important Features

- Transmission (EBV): **Contact with oropharyngeal secretions , saliva.**
- In developing countries, infections occur early in life; more than 90% of children are infected by age 6.
- **These infections in early childhood usually occur without any recognizable disease.**
- The inapparent infections result in permanent immunity to infectious mononucleosis (kissing disease).

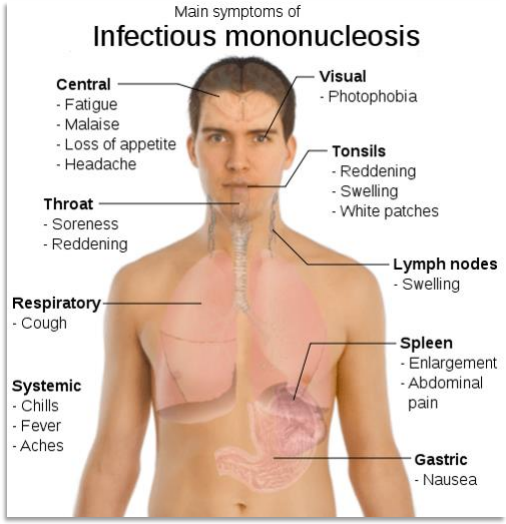
EBV Primary Infection-Pathogenesis & Pathology

- EBV is commonly transmitted by infected saliva and initiates infection in the oropharynx.
- Viral replication occurs in epithelial cells and B lymphocytes of the pharynx and salivary glands.
- Infected B cells spread the infection from the oropharynx throughout the body.

EBV Epidemiology

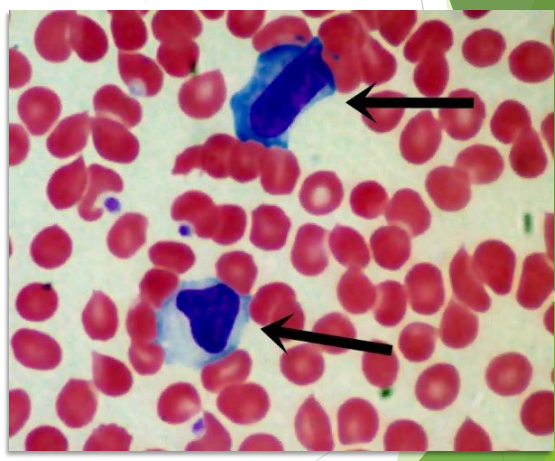
- Over 90% of adults being seropositive (had serologic evidence of previous infection) to EBV worldwide.
- **In developed countries, more than 50% of EBV infections are delayed until late adolescence and young adulthood. In almost half of cases, the infection is manifested by infectious mononucleosis (kissing disease).**

Infectious Mononucleosis (IM), Kissing Disease

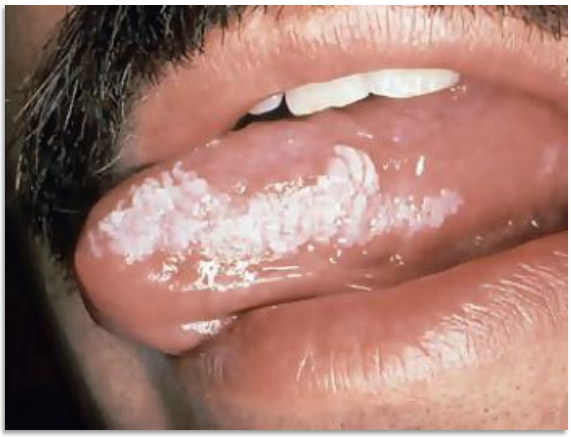


Infectious Mononucleosis (IM)

- The incubation period for IM is about 4 to 6 weeks.
- The peripheral blood shows leukocytosis, an increase in T cells but not B cells, and **atypical lymphocytes** (predominantly activated T cells having large amounts of cytoplasm).

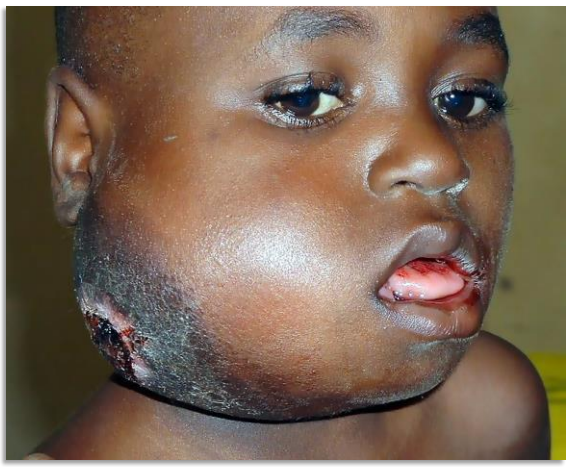


Oral Hairy Leukoplakia caused by EBV



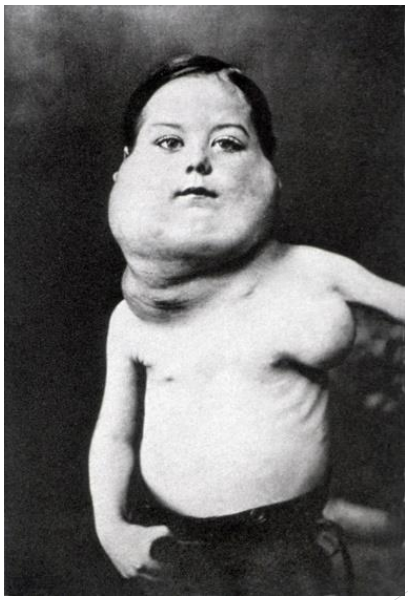
AIDS patients infected with EBV may exhibit **nonmalignant**, white-gray lesions on the tongue (hairy leukoplakia)

B cell lymphoma related to EBV

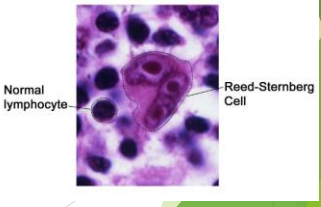


Hodgkin Lymphoma related to EBV

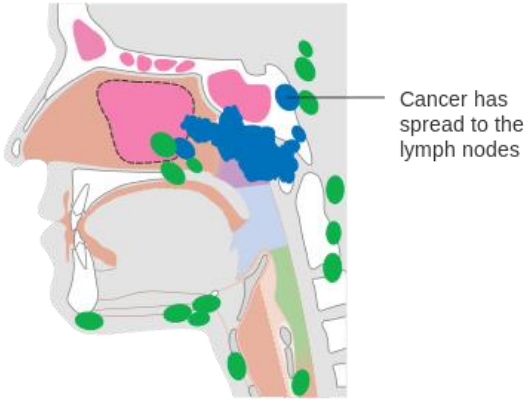
Hodgkin's lymphoma. *Photograph from 'Atlas of Clinical Medicine' (1892) by Scottish pathologist Byrom Bramwell.*



Hodgkin's lymphoma. Lymphoma marked by the presence of a type of cell called the Reed–Sternberg cell



Nasopharyngeal Carcinoma caused by EBV (HHV-4)

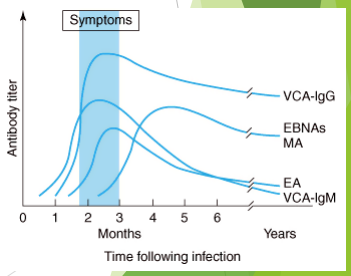


Human Oncoviruses

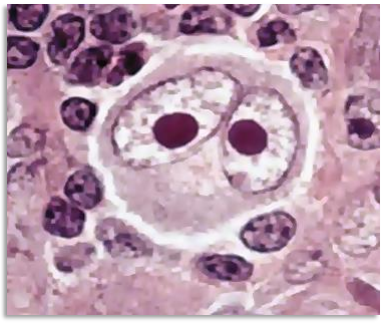
- Human herpes virus type 4 (HHV-4; EBV).
- Human herpes virus type 8 (HHV-8; Kaposi sarcoma herpes virus).
- Hepatitis B virus (HBV).
- Hepatitis C virus (HCV).
- Human T-lymphotropic virus 1 (HTLV-I).
- Human papillomaviruses (HPV) [HPV-16, HPV-18].
- Merkel cell polyomavirus.

IM Laboratory Diagnosis and Rx

- The diagnosis of IM in patients with typical symptoms is made by **a positive heterophile antibody**.
- Titers of EBV-specific antibodies (VCA, EA, MA and EBNA) are measured.
- Detection of EBV DNA in the blood can be useful.
- **Treatment of IM is supportive**. Contact sports should be avoided during the acute phase of the disease due to the risk of splenic rupture.



Cytomegalovirus (CMV)-Introduction



CMV-Taxonomy

- Order (*Herpesvirales*)
  - Family (*Herpesviridae*)
    - Subfamily (*Betaherpesvirinae*)
      - Genus (*Cytomegalovirus*)
        - Species (*Human betaherpesvirus 5*)

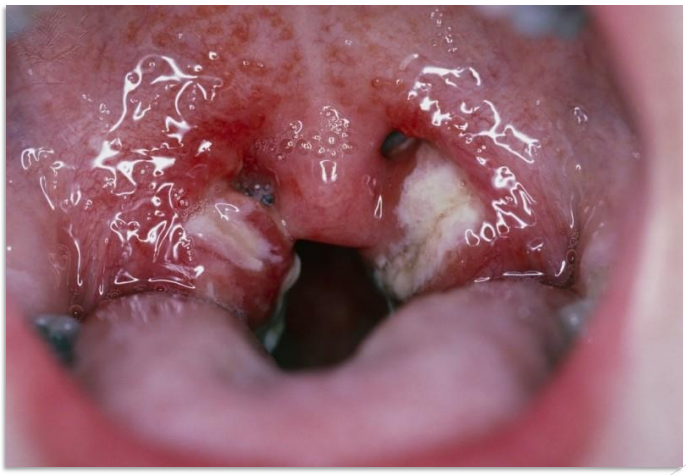
CMV-Important Features

- *Natural Host:* Human, monkeys.
- *Tropism:* Many cell types.
- *Latency:* Myeloid cells.
- *Cellular receptors:* Heparan sulfate among other candidates.
- *Geography:* Worldwide.

CMV-Important Features

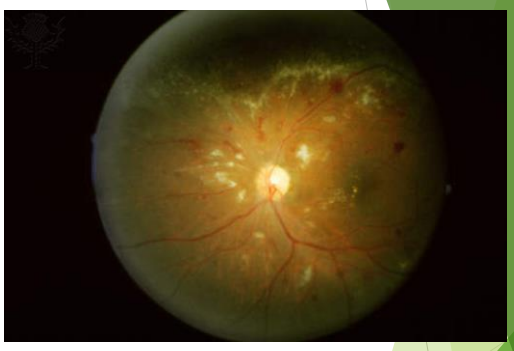
- *Transmission (CMV):* **Contact with urine, saliva.**
  Congenital.
  Sexual.
- Cytomegalovirus poses an important public health problem because of its high frequency of **congenital infections**, which may lead to severe congenital anomalies.
- **CMV is the most common congenital viral infection in the developed world, with an overall birth prevalence of approximately 0.6%.**

CMV (infectious mononucleosis like syndrome)



CMV-Immunocompromised Host

- **Pneumonia** is a frequent complication.
- Cytomegalovirus often causes **disseminated disease** in untreated AIDS patients.
- **Gastroenteritis** and **retinitis** are common problems, the latter often leading to progressive blindness.



Ophthalmoscope view of the retina of an AIDS patient showing the effects of a CMV infection

Congenital CMV Infection

- Approximately 10% of congenitally infected infants have signs and symptoms of disease at birth.
- **Symptomatic infants have a high risk for subsequent neurologic sequelae, including hearing loss, mental retardation, microcephaly, development delay, seizure disorders, and cerebral palsy**.
- Treatment of congenital CMV infection with antivirals should be initiated in infants with suspected disease.
- The cornerstone of antiviral therapy is **ganciclovir**.

CMV Laboratory Diagnosis

- **PCR assays** have replaced virus isolation for routine detection of cytomegalovirus infections. Cell culture methods of viral isolation are too slow to guide Rx.
- CMV produces a characteristic CPE (Massively enlarged "cytomegalic" cells are typical, besides **Owl's eye appearance** of inclusion bodies "intranuclear basophilic inclusions").
- Blood and urine are most commonly tested.
- **Serology:** Detection of viral IgM antibodies suggests a current infection.

Roseoloviruses-Introduction

- ✓ Both HHV-6 and HHV-7 are causative agents of **roseola infantum (exanthem subitum; sixth disease).**
- ✓ The pathogenic implications of their reactivation have not yet been described.

Roseoloviruses-Important Features

- ***Natural Host:*** Human.
- ***Tropism:*** **HHV-6:** T cells, B cells, natural killer (NK) cells, Monocytes-macrophages, epithelial cells and nerve cells.

  HHV-7: CD4+ T lymphocytes and epithelial cells of salivary glands
- ***Latency:*** Peripheral blood mononuclear cells (PBMCs).
- ***Cellular receptors:*** **HHV-6:** CD46.

  HHV-7: CD4.
- ***Geography:*** Worldwide.

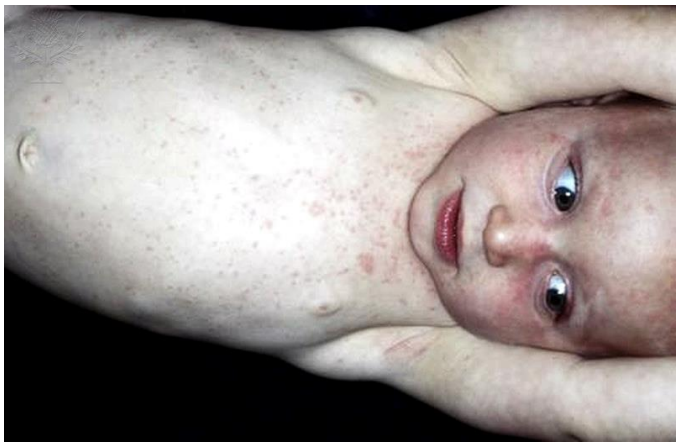
Roseoloviruses-Important Features

- *Transmission:* Respiratory, direct contact.
- Both viruses are ubiquitous and infect nearly all human beings in early childhood.
- Both viruses are implicated in many acute febrile illnesses and febrile seizures among infants.

Exanthem Subitum (Roseola Infantum, Sixth Disease)

- In the classic presentation, an infant develops sudden fever, which lasts for a few days, followed immediately by a rash that appears on the trunk and face and spreads to lower extremities as the fever subsides.
- Due to the high fever, the infection might be associated with **febrile seizures**.
- The disease is nearly always harmless, characterized by sudden onset with high fever and manifests as a typical exanthem in small children.
- Reports of HHV-6-caused illness in adults are rare and the clinical pictures described resemble mononucleosis.

Exanthem Subitum (Roseola Infantum, Sixth Disease)



Rash of Exanthem Subitum

Poxviridae-Introduction

- Poxviruses are a family of large, genetically **complex** viruses having no obvious symmetry.
- The agent of previous medical importance to humans, **variola virus**, was the cause of smallpox, the first infectious disease to be declared eradicated from the earth.
- The last known case was in Somalia in 1977.

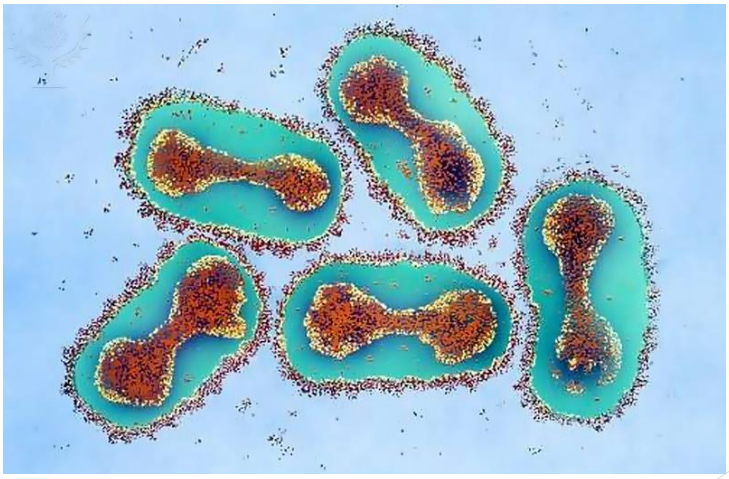
The factors that led to successful eradication of smallpox

1. The availability of an effective, **live attenuated** vaccine.
2. Variola virus was antigenically stable and **only a single antigenic type** existed.
3. The absence of asymptomatic cases or persistent carriers.
4. The absence of an animal reservoir.
5. The emotional effect of this highly lethal, disfiguring disease helping to gain public cooperation in the eradication efforts.

Structure & Classification

- The genome is a single linear **double-stranded DNA**, encoding more than 200 polypeptides. The virion is **enveloped**.
- The vertebrate poxviruses are related by a common nucleoprotein antigen, but are otherwise quite distinct.
- Humans are the natural host for variola and molluscum contagiosum virus (MCV), however, monkeypox, cowpox, and several other animal poxviruses can also cause human disease.

Structure & Classification



Color enhanced transmission electron micrograph (TEM) of the Smallpox virus (Poxviridae). Magnification: 42,000×.

Pathogenesis & Clinical Picture

- Variola viruses are transmitted aerogenically.
- The mucosa of the upper respiratory tract provides the portal of entry.
- From there, the pathogens enter the lymphoid organs and finally penetrate to the skin, where typical eruptions form and, unlike varicella pustules, **all develop together** through the same stages.

Clinical Findings

- The incubation period was 10–14 days.
- The onset was usually sudden.
- One to 5 days of fever and malaise preceded the appearance of the exanthems, which began as macules, then papules, then vesicles, and finally pustules. These formed crusts that fell off after about 2 weeks, leaving **pink scars** that faded slowly.
- The case-fatality rate reached 40%. Deaths were related bleeding, cardiovascular collapse, and secondary infections.

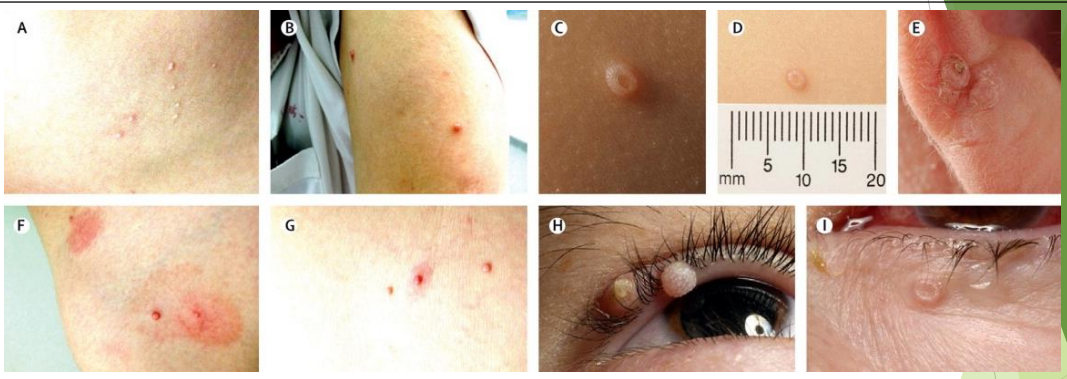
Epidemiology

- Transmission of smallpox occurred by contact between cases or inhalation of airborne virus.
- Smallpox was **highly contagious**.
- The virus was stable in the extracellular environment but was most commonly transmitted by respiratory spread.
- The dried virus in crusts from skin lesions could survive on clothes or other materials and result in infections.
- Smallpox is potentially a devastating biologic weapon because it is highly contagious and has a high case fatality rate.

Molluscum contagiosum virus (MCV)

- Molluscum contagiosum is a viral infection characterised by small, discrete, skin-coloured, dome-shaped papules.
- The number of individual lesions is generally fewer than 20.
- Rarely, molluscum contagiosum causes lesions on the palms and soles, or mucous membranes such as the lip, buccal mucosa or conjunctivae.
- MCV transmission occurs by direct contact, through contaminated fomites, or sexual activity.

Molluscum contagiosum virus (MCV)



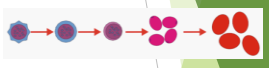
MC lesions on back of a 3-year-old patient (A). Lesions on arm of a 60-year-old patient (B). Single, non-inflamed lesion showing the characteristic **punctum** (C). Typical, non-inflamed lesion (D). MC on ear showing a haemorrhagic punctum (E). Inflamed lesions on shoulder of an 11-year-old patient (F,G). Two lesions on upper eyelid margin (H); Lower eyelid in a patient with MCV conjunctivitis (I)

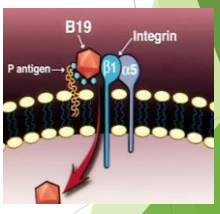
Parvoviruses-Taxonomy

- Order (Unassigned)
  - Family *(Parvoviridae)*
    - Subfamily *(Parvovirinae)*
      - Genus *(Erythrovirus)*
        - Species *(Primate erythroparvovirus 1; Parvovirus B19)*

Parvovirus B19-Important Features

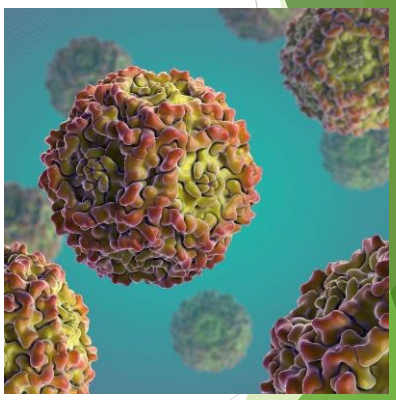
- *Natural Host:* Human.
- *Tropism:* Mitotically active erythroid precursor cells in bone marrow
- *Cellular receptors:* **Blood group P antigen**.
- *Transmission:* Respiratory, oral droplets.
- *Geography:* Worldwide.





Parvovirus B19-Important Features

- Parvoviruses are the smallest of the DNA viruses that infect humans.
- They are naked and icosahedral, with single-stranded, linear DNA.



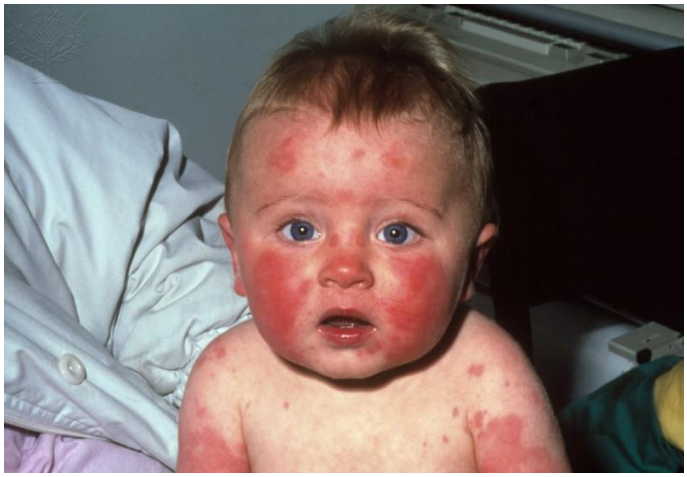
Pathogenesis

- Transmission of parvoviruses is by the respiratory route.
- A high titered viremia lasting a few days follows about one week after infection, during which time virus is also present in throat secretions.
- A specific antibody response occurs rapidly, resulting in suppression of the viremia.

Clinical Disease (Erythema infectiosum, fifth disease)

- A childhood exanthema with characteristic rash ("slapped cheek" appearance).
- It occurs about 2 weeks after initial exposure, when the virus is no longer detectable. It is apparently **immune system–mediated**.
- Another complication accompanying B19 infection is an acute **arthritis** that usually involves joints symmetrically. This is considerably more frequent in adults than in children, and usually resolves within several weeks.

Clinical Disease (Erythema infectiosum, fifth disease)



Fifth disease. Red rash on an infant's face and arms, known as **'slapped cheek' or Fifth disease**. Also called erythema infectiosum

Clinical Disease (Congenital Infection)

- Spontaneous **abortion** rate is elevated in women having a primary infection during the first trimester.
- Primary infection during the second or third trimester is associated with **hydrops fetalis** (fetal edema due to anemia mandating the fetal heart to pump greater blood volumes).

Clinical Disease (Aplastic crisis)

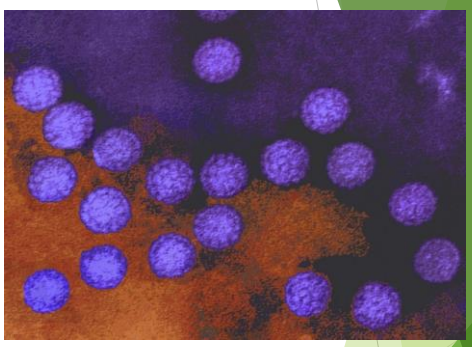
- Chronic, progressive bone marrow suppression results from B19 infection of immunocompromised patients unable to mount an immune response capable of eliminating the virus.
- It is most dangerous in patients with pre-existing bone marrow deficits; e.g. Sickle cell disease.

Epidemiology Dx and Rx

- Up to 60% of all adults and 90% of elderly people are seropositive.
- The most sensitive tests detect viral DNA. Available tests are PCR-based.
- Fifth disease and transient aplastic crisis are treated symptomatically. The latter may require transfusion therapy.

Polyomaviridae-Introduction (not for the exam)

- (Gk. Poly: many, multiple; Oma, tumors).
- Naked viruses.
- Icosahedral
- Contain double-stranded DNA genome.
- Able to establish latency.

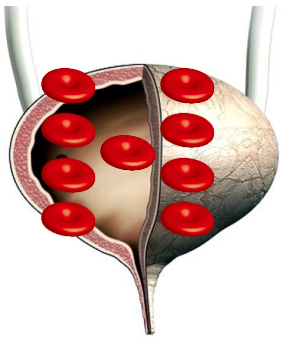


BK virus. Coloured transmission electron micrograph (TEM) of BK virus particles.

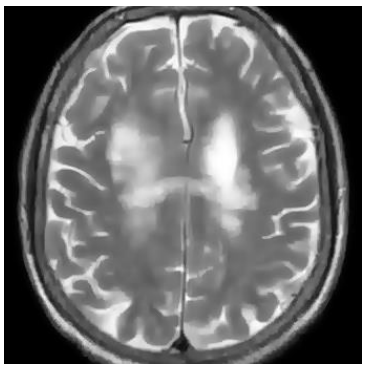
Polyomaviridae-Taxonomy (not for the exam)

- Family *(Polyomoviridae)*
  - Genus *(Alphapolyomavirus)*
    - Species *(BK virus (BKV))*.
    - Species *(JC virus (JCV))*.
    - Species *(Merkel cell polyomavirus (MCPyV))*.

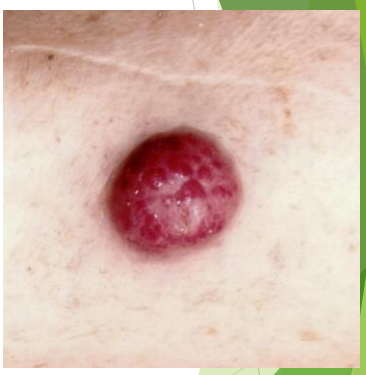
Clinical Conditions (not for the exam)



BK virus: Hemorrhagic cystitis



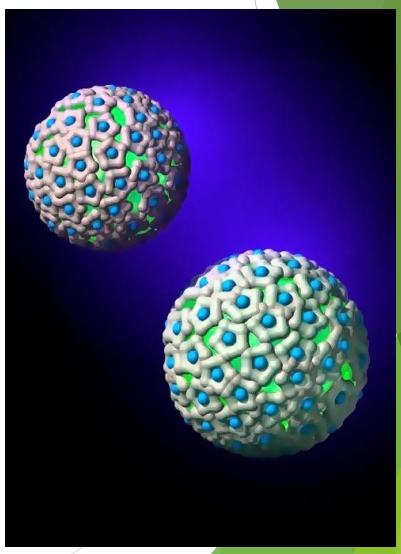
JC virus: Progressive multifical leukoencephalopathy (PML)



MCPyV: Merkel cell carcinoma

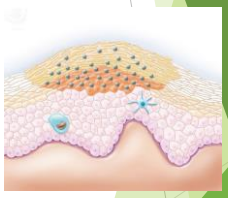
Papillomaviridae-Introduction

- Double-stranded DNA viruses.
- Naked.
- Icosahedral.
- Oncovirus.



Papillomaviridae-Important Features

- *Natural Host:* Human.
- *Tropism:* Epithelial cells of skin, mucous membranes
- *Cellular receptors:* Heparan sulfate.
- *Transmission:* Sexual, indirect & direct contact.
- *Geography:* Worldwide.



Pathogenesis

- HPVs exhibit great tissue and cell specificity, **infecting only surface epithelia of skin and mucous membranes.**
- The HPVs within each of these tissue-specific **types** have varying potentials for causing malignancies:

1) Virus types that produce lesions having a **high risk** of progression to malignancy, such as in cervical carcinoma.
2) Types that produce mucosal lesions that progress to malignancy with lower frequency, causing, anogenital warts and laryngeal papillomas.
3) Other virus types that are associated only with **benign lesions** (for example, common, flat, and plantar warts).

Introduction to Microbiology for M.D. Students

Viral Hepatitis, HIV and AIDS-Material for the exam

University of Jordan

School of Medicine

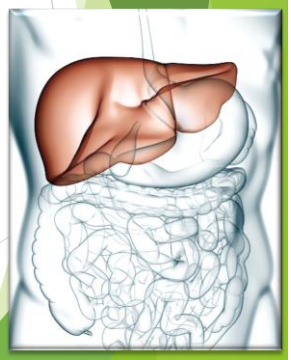
Department of Pathology, Microbiology and Forensic Medicine

Section of Microbiology and Immunology

Malik Sallam, MD, PhD

Viral Hepatitis-Introduction

- Viral hepatitis is a systemic disease primarily involving the liver.
- Most cases of acute viral hepatitis are caused by one of the following agents: HAV, HBV, HCV, or HEV.
- Hepatitis viruses produce acute inflammation of the liver, resulting in a clinical illness characterized by fever, nausea, vomiting, and jaundice.
- Regardless of the virus type, **identical histopathologic lesions are observed in the liver during acute disease**.



Viral Hepatitis-Summary

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Family	*Picornaviridae*	*Hepadnaviridae*	*Flaviviridae*	Unclassified	*Hepeviridae*
Envelope	No	Yes (HBsAg)	Yes	Yes (HBsAg)	No
Genome	Positive ssRNA	dsDNA	Positive ssRNA	Negative ssRNA	Positive ssRNA
Stability	Heat- and acid-stable	Acid-sensitive	Acid-sensitive	Acid-sensitive	Heat-stable
Transmission	Fecal-oral	Parenteral	Parenteral	Parenteral	Fecal-oral
Chronic disease	Never	Often	Often	Often	Rare?

Hepatitis A - Clinical & Lab. Findings

- Incubation period: 10–50 days (average, 25–30).
- Principal age distribution: Children, young adults.
- Seasonal incidence: Throughout the year but tends to **peak in autumn**.
- Route of infection: Predominantly **fecal–oral**.

Hepatitis A - Clinical & Lab. Findings

- Onset: Abrupt (sudden).
- Fever: Common.
- Duration of aminotransferase elevation: 1–3 weeks.
- Complications are uncommon, **no chronic state**.
- Patients with inapparent or subclinical hepatitis have neither symptoms nor jaundice.

Hepatitis A - Clinical & Lab. Findings

- Other patients can develop anicteric hepatitis or icteric hepatitis.
- Symptoms ranging from mild and transient to severe and prolonged can accompany anicteric or icteric hepatitis.
- Most patients recover completely; however, some develop fulminant hepatitis and die.

Hepatitis A - Dx, Rx & Prevention

- LFT (liver function tests), IgM anti-HAV (antibody detetction).
- No specific treatment for acute viral hepatitis exists, and hospitalization is not ordinarily indicated. Therapy should be supportive and aimed at maintaining comfort and adequate nutritional balance.
- Formaldehyde inactivated vaccines are available worldwide.

Hepatitis E Virus (HEV)-Introduction

- Previously labeled **e**nterically transmitted non-A, non-B hepatitis, HEV is an **e**nterically transmitted virus that occurs primarily in India, Asia, Africa, and Central America; in those geographic areas, HEV is the most common cause of acute hepatitis.
- This agent, with epidemiologic features resembling those of hepatitis A, nonenveloped, HAV-like virus with a 7.6 kb, single-strand, positive-sense RNA genome.

Hepatitis E-Pathogenesis

- Entry of the virus into the host is believed to be primarily by the **fecal-oral** route.
- The incubation period ranges from 2 weeks to 2 months.
- HEV replicates in the cytoplasm of hepatocytes. **No chronic state after acute infection**.

Hepatitis E-Pathogenesis

- More important, however, is the severity of hepatitis E in **pregnant women**, which may reach 20%.
- The reason for the excessive mortality of hepatitis E in pregnancy is unknown, although a high viral load and abnormalities of progesterone signaling pathways have been suggested.

Hepatitis B Virus (HBV)-Background

- HBV is **a DNA virus** with a peculiar genome that is a circular **partially double-stranded DNA** of about 3.3 kb (slight length differences are observed in different genotypes).
- HBV is the only human virus that belongs to the family *Hepadnaviridae*, while other animal viruses have been identified that belonged to the same family of viruses which can infect mammals and birds with characteristic tropism for **hepatocytes.**

Epidemiologic features and transmission of HBV

- The percutaneous transmission is the major route for HBV infection. Other major routes of transmission include sexual spread and mother-to-child transmission (MTCT).
- In areas with high endemicity (sero-prevalence ≥8%, e.g. Southeast Asia), MTCT represents a frequent mode of spread with its subsequent high prevalence of chronicity.

Natural history and clinical features of hepatitis B

- HBV can cause both acute and **chronic** infections, with age as one of determinants of chronicity.
- Fulminant hepatitis can follow acute infection.

Diagnosis, treatment and prevention of hepatitis B

- After HBV infection, the first markers of the disease is the appearance of viral DNA in the liver and plasma together with circulating hepatitis B surface antigen (**HBsAg**). High levels of viremia is followed by rise in the level of markers of hepatocyte damage (mainly ALT) and the appearance of clinical features (fever, malaise and jaundice).

Diagnosis, treatment and prevention of hepatitis B

- **The persistence of HBsAg beyond 6 months marks HBV chronicity**.
- HBcAb (core antibodies of IgM type) appears within the first two weeks after the appearance of HBsAg and preceding HBsAb (surface antibody).
- The window between decline of HBsAg and rise HBsAb is associated **with HBcAb as the only serologic evidence of infection**.
- Clearance is associated with the appearance of HBsAb.

Diagnosis, treatment and prevention of hepatitis B

- Multiple options are available for treatment of chronic hepatitis B including IFNs (interferon) and several nucleotide and nucleoside analogs with the goal of reducing the viral load to an undetectable level and to reach HBsAg clearance.
- For prevention of HBV infection, an effective vaccine (recombinant HBsAg) has been available from mid-1980s, with many countries worldwide implementing universal vaccination of infants.

Hepatitis D Virus (HDV) - Background

- Delta hepatitis was first recognised following detection of a novel protein, delta antigen (HDAg), by immunofluorescent staining, in the nuclei of hepatocytes from some patients with hepatitis B.
- HDV is now known to be defective and require a helper function from HBV for its transmission. HDV is coated with HBsAg, which is needed for release from the host hepatocyte and for entry in the next round of infection.

Hepatitis D Virus (HDV)

Two types of infection are described:

-Co-infection: Where a person who is susceptible to HBV is exposed to someone who is co-infected with HBV and delta virus, this results in acute co-infection with both the viruses at the same time.

-Super-infection: When an HBV carrier is exposed to infected blood from co-infected patients then the exposure results in super-infection of the existing HBV infection with delta virus; this may result in development of acute hepatitis (due to delta virus) in an HBV chronic carrier.

Hepatitis C Virus (HCV)-Background

- Before the identification of HCV, it was evident that the culprit infectious agent responsible for the majority of “non-A, non-B hepatitis (NANBH)" cases was a novel virus that is unrelated to other hepatitis viruses known at that time, namely HAV, HBV, HDV and HEV.

HCV Transmission

The major route of HCV transmission worldwide is the exposure to contaminated blood mainly through **IDU** (injection drug abuse) particularly in the high-income countries. After the introduction of effective screening of blood/blood products used for transfusion, health-care-related spread of HCV became less common.

HCV Transmission

Other lower-risk modes of transmission include high risk sexual behaviour, vertical transmission, health-care associated infections (percutaneous exposure through needlestick injuries, haemodialysis, surgeries or dental procedures), intrafamilial spread, tattooing, piercing and acupuncture. The per-act risk of infection is mainly related to the volume of inoculum together with the viral load of the source of infection, with transfusion as an efficient route.

Diagnosis of HCV Infection

- The diagnosis of HCV starts by **serologic screening.**
- The serologic assays confirm the history of HCV past infection, nevertheless, the diagnosis of ongoing infection relies on **nucleic acid testing** which is also used to monitor response to treatment.

Treatment of Chronic HCV Infection

- The traditional treatment of HCV relied on IFN-based regimens (with ribavirin) that were limited by severe adverse effects and variable efficiency depending on variables like HCV genotype.
- The novel therapeutic options of HCV in the form of **direct-acting antivirals (DAAs)**, have resulted in rising hope among clinicians and patients for better response, less side effects and shorter duration of therapy.

Diagnosis, treatment and prevention

Class	HCV target	Drugs
Protease inhibitor	NS3	Simeprevir, Boceprevir, Telaprevir.
Nucleotide inhibitor	NS5B	Sofosbuvir.
Non-nucleotide inhibitors	NS5B	Dasabuvir, Beclabuvir.
NS5A inhibitors	NS5A	Daclatasvir, Velpatasvir.

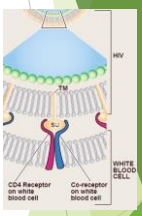
Prevention of Hepatitis C (not for the exam)

- Due to *absence of an effective vaccine to HCV* infection so far, prevention of transmission relies on identifying individuals at risk and consulting on behavioural changes to decrease the likelihood of forward transmission. In the low-income settings, strict testing of blood/blood products before transfusion is of prime importance.
- In high-income countries where IDU represents the major risk factor for HCV spread, awareness, behavioural changes, treatment as prevention (TasP), opioid substitution treatment (OST) and needle exchange program (NEP) represent important intervention measures to control the HCV epidemics.

HIV, Important Features

- *Natural Host:* Human.
- *Tropism:* CD4+ T cells, macrophages and dendritic cells
- *Cellular receptors:* CD4 + (CCR5 and/or CXCR4)
- *Geography:* Worldwide (HIV-1 group M)

  West Africa (HIV-2)



HIV-1 Transmission

- HIV-1 is a **blood-borne virus** (i.e. it can be transmitted through *transfusion*, *needlestick injury* and *IDU*) and the infection can be considered an **STI** (occurring through homosexual and heterosexual practices via vaginal, penile and anal mucosa).
- **Vertical transmission** can occur in utero, perinatally and through breast milk of infected mothers.
- Nowadays, the most common mode of transmission globally is **HET** contact but different regions differ in the most common route (e.g. **MSM** in US and Western Europe, **IDU** in Former Soviet Union countries and **HET** in sub-Saharan Africa).

HIV-1 Pathogenesis

- The distinctive feature of HIV-1 infection is the progressive quantitative and qualitative deficiency of **CD4+ T cells**.
- After HIV-1 inoculation, the virus infects its target cells, mostly macrophages through binding of **gp120** (part of ENV) to **CD4** and chemokine receptors **CCR5** or **CXCR4**.
- The virus starts to establish the infection for about 10 days locally before **systemic** spread.
- Subsequent virus spread into the lymphoid tissues including the gut-associated lymphoid tissue (**GALT**), ends-up in the establishment of infection chronically.

HIV-1 Pathogenesis

- Viremia follows, which remains at high levels for about 8–12 weeks, coinciding with **mononucleosis-like features** in a majority of infected individuals.
- **The significant decline of CD4 cells at this phase is related to loss of memory cells in the GALT**.
- The adaptive immune response takes over at this stage to control viral replication manifested in the decline of viral load to a nadir "**viral set-point**", which fluctuates at low level throughout the clinical latency.
- **HIV-1 set-point** is considered an important **prognostic marker for assessment of disease progression**.

Clinical features

- **Primary infection (first few months):** Nonspecific and resemble those of infectious mononucleosis.
- **Clinical latency (3-20 years, average 8-10 years):** The majority of HIV-1 infected individuals remain **asymptomatic** during the clinical latency period, nevertheless, *generalized lymphadenopathy* might persist from the primary infection period.
- **AIDS:** The diagnosis of AIDS is made at **CD4 T cell count of less than 200/µL** or **the presence of an AIDS defining condition** (extrapulmonary TB, toxoplasmosis, cryptococcosis, esophageal candidiasis, lymphomas, etc.).

Diagnosis of HIV infection (not for the exam)

- Screening for HIV-1 infection relies on **enzyme immune assays.**
- This is followed if positive by a confirmatory test, mostly **western blot** or detection of HIV-1 RNA.

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