Herpesviruses

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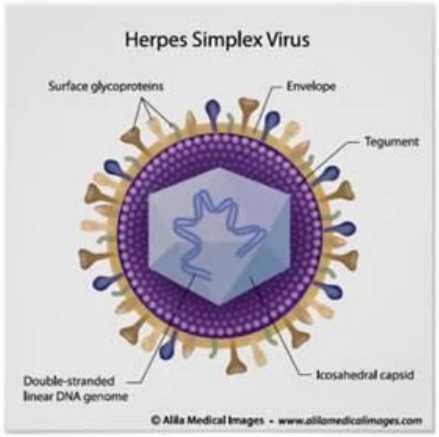
Herpesviridae (Herpesviruses)

- **Herpesviridae (Herpesviruses)** include: Herpes simplex, herpes zoster, Herpes virus 8 (Kaposi sarcoma-associated herpesvirus) cytomegalovirus (CMV), Epstein-Barr virus (EBV)



- Double stranded DNA viruses
  - Linear dsDNA genomes
- Enveloped polyhedral viruses (150-250nm)
- Replicate in the nucleus, encapsulation occurs in the nucleus and membrane is acquired on budding
- Medium sized viruses, cause chickenpox, shingles, Burkitt's lymphoma, infectious mononucleosis, CMV causes pneumonia and brain lesions in immunocompromised individuals, EBV causes Burkitt’s lymphoma.

Herpesviruses (Herpesviridae)

- All Herpesviruses have capacity to persist in their host indefinitely (chronic infection)
  - Double stranded DNA persist as nuclear episomes (unintegrated DNA)
  - Varicella-Zoster virus (chickenpox) and herpes simplex viruses establish latent infection in neurons
  - On reactivation Varicella causes herpes zoster (shingles) and chickenpox; herpes simplex type 1 causes labial herpes, herpes simplex type 2 is responsible for genital herpes.
  - Cytomegalovirus (CMV), Epstein-Bar virus (EBV) and human herpes virus type 6 (HHV-6) cause chronic infections in lymphocytes
    - EBV causes infectious mononucleosis and is associated with some cancers, carcinoma and lymphoma.
    - HHV-6 causes numerous skin rashes in children
- Increasing important because of HIV/AIDS and immunosuppression for organ transplant or cancer treatment

Human Herpesviruses

Subfamily/genus	Official name	Vernacular name	Biological properties
Alphaherpesvirinae			
Herpes simplexvirus	Human herpesvirus 1	Herpes simplex virus 1	Fast growing, cytolitic and latent in neurons
	Human herpesvirus 2	Herpes simplex virus 2	
	Cercopithecine Herpesvirus 1	Simian herpes B virus	
Varicellovirus	Human herpes virus 3	Varicella-zoster virus	
Betaherpesvirinae			
Cytomegalovirus	Human herpesvirus 5	Cytomegalovirus	Slow growing, cytomegallic, latent in salivary glands, kidneys
Roseolovirus	Human herpesvirus 6		Latent in macrophages and lymphocytes
Gammaherpesvirinae			
Lymphocryptovirus	Human herpesvirus 4	Epstein-Barr virus	Lymphoproliferative, latent in B lymphocytes
	Human Herpesvirus 8	Kaposi sarcoma-associated herpesvirus (HHV8)	

Herpes simplex viruses

- Responsible for a wide range of disease including gingivostomatitis, keratoconjuctivitis, encephalitis, genital disease, disease in neonates
- HSV establishes latent infections in nerve cells and recurrences are common
- Causes cytolic infections
  - Pathology associated with necrosis and inflammation
  - Similar to varicella zoster disease

Primary infection

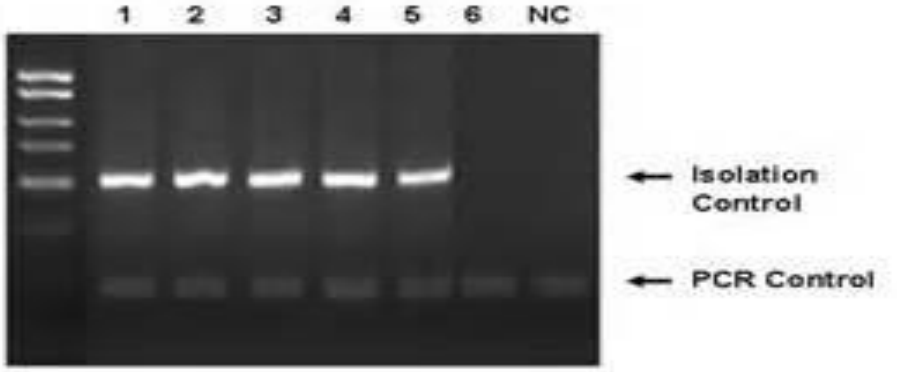
- Transmission is by contact (mucosal surfaces or broken skin, droplets or saliva)
- Initial replication in the oropharynx but virus infects local nerve ending and is transported to the CNS (dorsal root ganglia) by retrograde axonal transport (to establish latency)
- Disease is mild and often asymptomatic
  - Viremia occurs in immunocompromised individuals

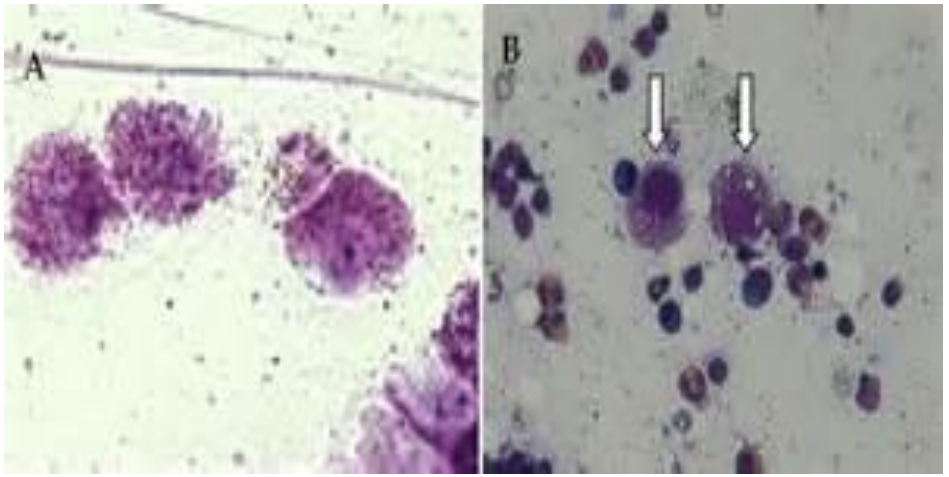
Latent infection

- Virus in dorasl root ganglia (non-replicating)
- Reactivation: virus takes axonal root to the periphery
- Manifestations include cold sores near the lip

Diagnosis

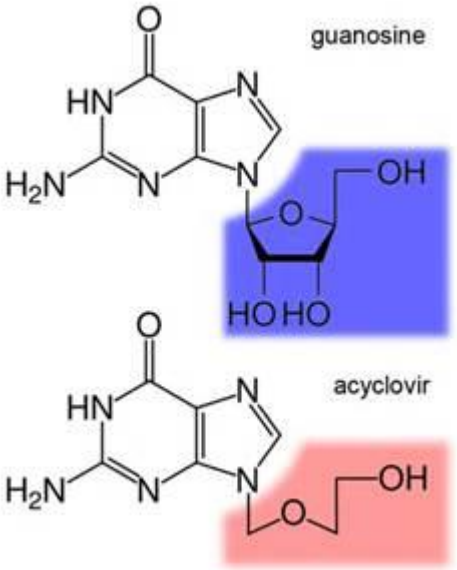
- PCR
- Virus isolation
- Cytopathology
  - Giemsa stain
- Serology
  - EIA





Treatment

- Inhibitors of DNA polymerase
  - Acyclovir



Cytomegalovirus (CMV)

- Ubiquitous herpesvirus
  - Most common cause of congenital infection
  - Disease ranges from generalized infection
  - Severe disease is found in immunocompromised adults

- Properties
  - Largest genetic content of all human Herpesviruses
  - Very species specific
  - Replicates in fibroblasts and epithelial cells
  - Cytopathic effect: cell enlargement

Transmission

- Close contact
- Incubation period of 4-8 wks
- Causes systemic infection
  - Causes infectious mononucleosis-like disease
  - Most infections are subclinical
  - Virus shed in urine and from pharynx
  - Establishes latent infection
  - Dampens cell mediated immunity and allows for viral persistence
  - Pneumonia is the most common symptom in immunocompromised patients

Epstein –Barr Virus

- Main cause of acute infectious mononucleosis
- Associated with pharyngeal carcinoma, Burkitt lymphoma, Hodgkin's and non-Hodgkin’s lymphoma and other lymphoproliferative disorders, and gastric carcinoma
- Infections B cells (transforms/immortalizes B cells)
- Establishes latency and reactivation is common in immunocompromised individuals

Human Herpesvirus 8 (HHV8)

- First identifies in 1994 in Kaposi sarcoma specimens
  - Kaposi sarcoma herpesvirus (KSHV)

- KSHV is lymphotropic
- KSHV is responsible for KS, vascular tumours and body cavity-based lymphomas
- Transmission is through sexual intercourse, vertically, blood and organ transplants, and contact of oral fluids
- Incidence of KS has reduced in HIV-infected patients on cART

Varicella-zoster virus

- Varicella-zoster virus causes two almost universal human diseases:
  - Varicella (chickenpox), a childhood exathem and herpes zoster (shingles), a disabling disease of aged person or immunocompromised individuals

- **Pathogenesis and immunity**
  - Virus enters by inhalation and replicates respiratory mucosa
  - Incubation period of 10-20 days
  - Dissemination occurs via mononuclear leukocytes and endothelial cells
  - Rash result from multiplication of virus in epithelial cells in the skin.
  - Herpes zoster occurs when Varicella virus in sensory ganglion is reactivated and descends the sensory nerve within the axon.
    - Decline in cell-mediated immunity is thought to precipitate herpes zoster attacks

Varicella (chickenpox)

- Rash happens suddenly with or without fever
- Eruption occurs on the trunk then spreads to head and limbs
- Very itchy lesions (scratching); can lead to secondary bacterial infection
- Painful ulcerating vesicles may develop in mucous membranes (mouth or vulva)
- Neurological complication are rare but more serious (1:1000 develop encephalitis, other complications include Guillain-Barre syndrome and Reye's syndrome)
- Disease may be disseminated to lungs (pneumonia), liver and brain
  - Disease is severe in women with primary infection and infants born to mother who had no previous infection (no maternal antibodies against Varicella)

VARICELLA (CHICKENPOX)

Herpes Zoster

- Results from reactivation of virus in the sensory ganglion following attack of chickenpox many years earlier
- Vesicles are usually unilateral and confined to area of the skin innervated by particular sensory ganglion (*zoster*, gird le) on the trunk or face involving the eye, scattered lesions outside the dermatome may occur
- Pan is often severe for up to a few weeks but neuralgia may persist for months
- Motor paralysis and encephalomyelitis are rare complications
- Disseminated disease may be seen in cancer patients or immunocompromised patients

Herpes Zoster

Diagnosis

- Clinical features of Varicella and herpes zoster are so distinctive that laboratory diagnosis is rare
- Microscopy using skin smears to demonstrate characteristic intranuclear inclusions within multinucleated giant cells
  - Or use of monoclonal fluorescent antibody
- EIA to demonstrate Varicella virus antigens
- PCR can be used to amplify Varicella DNA isolated from virions in the vesicle fluid.
- Recent infection can be confirmed by rising titer of IgM using EIA

Epidemiology and control

- Varicella occurs throughout the year but most prevalent in late winter and spring
- Epidemic occur among susceptible children (schools and hospitals)
- **Passive immunization**: zoster immunoglobulin from convalescent zoster patients
  - Given to nonimmune pregnant woman or immunocompromised individuals who come into contact with Varicella within 3 days.
- **Active immunization (vaccination):** live attenuated vaccine from attenuated Oka strain of Varicella virus (made by serial passage in cultured human and guinea pig fibroblasts); protection is lower in children and immunocompromised patients. Vaccine strain may establish latent infection in the dorsal ganglia and get reactivated later on causing zoster but this reactivation is rare following natural varicella infection.
- **Chemotherapy:**
  - Can be managed by prevention of secondary bacterial infection
  - Pneumonitis or herpes zoster involving the eye needs treatment with intravenous or oral acyclovir