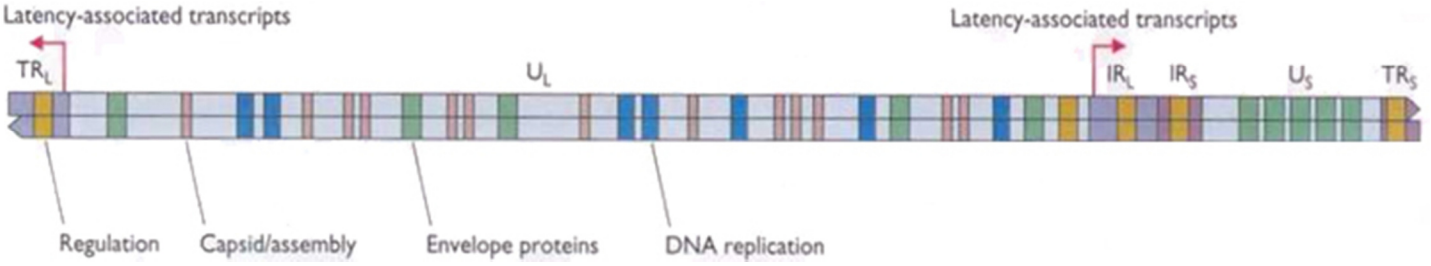
Herpes viruses

Introduction

The Herpetoviridae family is a complicated family of viruses. In this family we have 25 different viruses which infect both humans and different species of animals. Only 8 of the viruses are known to cause infections in humans. Each one causes different clinical manifestations which can be seen on a daily basis in hospitals.

Structure

Herpesviruses all share a common structure- all are enveloped and have a relatively large double-stranded, linear DNA genome. They are complicated because they contain so many different genes that control different functions of the virus. If you look at the genomic structure of the DNA of the herpes simplex virus, you can see different genes controlling different functions of the virus from Regulation to Transcription to Translation to Maturation and so on. These groups of viruses have the property of invading and replicating in nervous cells, while no other virus can invade the CNS and replicate to cause pathology in the CNS.



After replication in the CNS these viruses will go dormant and cause a latent infection due to the presence of latency associated transcripts. It means that during the replication cycle of these viruses in the CNS, they produce a transcript (i.e. the latency transcript) for the viruses to become latent in the CNS (it will sleep in the CNS) for a while and then reactivated when the immune system is suppressed. The human herpes viruses are the following:

Viruses of humans	Common name	Subfamily
Human herpes virus 1	Herpes simplex type 1	Alpha
Human herpes virus 2	Herpes simplex type 2	Alpha
Human herpes virus 3	Varicella-zoster	Alpha
Human herpes virus 4	Epstein-Barr	Gamma
Human herpes virus 5	Cytomegalovirus	Beta
Human herpes virus 6/7	exanthum subitum roseola infantum	Beta
Human herpes virus 8	Kaposi's Sarcoma-associated	Gamma

These three stages produce alpha, beta and gamma proteins. These proteins (especially alpha and beta) are acting as enzymes to proceed with the replication cycle.

- **Immediate early transcription** produces alpha proteins
- **Delayed early transcription** produces beta proteins
- **Late stage transcription** is concerned with development, maturation and release of the virus from the infected cells.

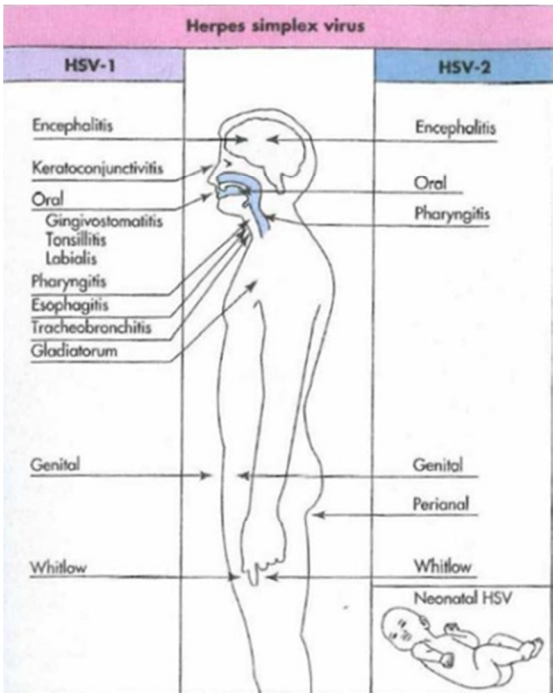
Subfamilies

- *Three* of the viruses (Herpes simplex type 1 & 2 and Varicella-zoster) are in the **alpha** subfamily and usually infect epithelial cells.
- **Cytomegalovirus** (along with human herpesvirus 6/7) belongs to the **beta** subfamily; **CMV** is an important virus which can cause congenital abnormalities.
- **Epstein - Barr virus** (along with human herpesvirus 8) belongs to **gamma** subfamily; **EBV** has been isolated from AIDS patients who had Kaposi's sarcoma.

We can distinguish these viruses according to their target cells, site of latency (usually neurons) and means of spread

Subfamily	Virus	Primary target cell	Site of latency	Means of spread
Alpha-Herpesvirinae				
Human herpesvirus 1	Herpes simplex type 1 (HSV-1)	Mucoepithelial	Neuron	Close contact
Human herpesvirus 2	Herpes simplex type 2 (HSV-2)	Mucoepithelial	Neuron	Close contact
Human herpesvirus 3	Varicella zoster virus (VZV)	Mucoepithelial	Neuron	Respiratory & close contact
Beta-Herpesvirinae				
Human herpesvirus 5	Cytomegalovirus (CMV)	Monocyte, lymphocyte, and epithelial cells	Monocyte, lymphocyte, and ?	Close contact, transfusions, tissue transplant, and congenital
Human herpesvirus 6	Herpes lymphotropic virus (HHV6)	T lymphocytes and ?	T lymphocytes and ?	Respiratory and close contact ?
Human herpesvirus 7	Human herpesvirus 7 (HHV7)	T lymphocytes and ?	T lymphocytes and ?	?
Gamma-Herpesvirinae				
Human herpesvirus 4	Epstein-Barr virus (EBV)	B lymphocyte and epithelial cells	B lymphocyte	Close contact (kissing disease)
? indicates that other cells may also be the primary target or site of latency.				

Herpes simplex **type 1** usually causes infections from the waist-line and above (Encephalitis, Keratoconjuctivitis, Gingivostomatitis, Tonsilitis, Labialis…etc) while **type 2** causes infections from waist-line and below (genital, perianal and neonatal herpes). Sometimes Herpes Simplex type 1 may cause genital infections and *whitlow* (infection of the fingers most commonly contracted by dental workers and medical workers exposed to oral secretions).



Immune Response to Herpes Infections

- **Interferon** is the first line of defense. Then we have the humoral antibody (the neutralizing antibody). Then we have complement-mediated lysis of infected cells. The neutralizing antibodies can be secreted with the milk so breastfeeding is very important for infants.
- **Cell-Mediated (T-lymphocyte) immunity** is the most important arm of immunity against herpes viruses and even if there is a defect in humoral immunity such as in agammaglobulinemics, they can recover from infection if they have normal T cell functions.
- Apart from the interferon we have the cytotoxic T-lymphocytes, natural killer cells, macrophages…etc

Neurovirulence and Latency in HSV and VZV

Herpes simplex and varicella zoster viruses have two unique biologic properties, which is the capacity to invade and replicate in the CNS.

- Virus lies dormant (*latent infection*) for a period of time but may become reactivated (*due to immune suppression*) even in the presence of neutralizing antibodies because they are not as effective as T-lymphocytes.
- Most studies indicate that the **sensory ganglia** are the source of virus that produces recurrent skin lesions- **trigeminal** ganglia in **type 1** and **sacral** ganglia in **type 2** and some of the dorsal ganglia for the varicella-zoster virus

Neurolatency hypotheses

- **Dynamic state:** persistence of low levels of infectious virus in sensory ganglia, neurons may or may not be killed. This leads to retrograde vs anterograde transport of virus through peripheral sensory nerve endings.
- **Static state:** DNA of virus is maintained in a non-replicating state at some extrachromosomal site in neuron or is integrated into cellular DNA.

Chemotherapy

- **HSV and VZV:** acyclovir (*aka* Cyclovir, Zovirax) is effective because these viruses contain thymidine kinase enzyme.
- **CMV:** ganciclovir; phosphonoacetate, interferon
- **NOTE:** the chemotherapy can't destroy the dormant stage of the viruses

Agents that inactivate the viruses

- Since the viruses have a lipid enveloped, agents such as ethyl ether, chloroform, glutaraldehyde can inactivate the virus by dissolving the envelope.

Immunologic approaches

- There is no vaccination for herpes simplex type 1 & 2, but we have a vaccine for Varicella-zoster (chicken pox) which is given with MMR (*called MMRV*) in US and Europe.

Diseases

The viruses cause a **primary** infection, then they become dormant, after that they are reactivated to cause a **recurrent** infection.

Virus	Pathogenesis	Symptoms	Target Group
HSV-1	Primary infection	Pharyngitis, Tonsillitis, Gingivostomatitis Eczema herpeticum Keratoconjuctivitis	Children & young adults Atopics Young adults
HSV-2	Primary infection	Vulvovaginitis, Herpes progenitalist Neonatal infections	Children & young adults Newborns
HSV-1	Recurrent infection	Herpes labialis, Keratoconjuctivitis, Encephalitis	Children & young adults
HSV-2	Recurrent infection	Herpes genitalis, Meningoencephalitis	Children & young adults

- **HSV isolated from lesions occurring above the waistline is usually type 1 and HSV isolated from sites below the waistline is usually type 2.** Nonetheless, because of oral-genital contact, either type of virus may be found in either location.
- **Primary HSV-1 infections are most common in childhood.** The usual manifestation in young children is gingivostomatitis; in adolescents it is tonsillitis or pharyngitis.
- **The prevalence of genital herpes bears a strong relationship to sexual promiscuity.** Genital HSV-2 infections are on the increase and are now second in frequency only to gonorrhea.

HSV Diseases:

Primary Infections:

1) **Gingivostomatitis (caused by type 1)**: affects children 1-6 years old. No seasonal distribution. Accompanied by fever, sore mouth and lymphadenopathy.
2) **Vulvovaginitis (type 2)**: involves mucous membranes and skin of the labia and lower vagina. Ulcers are accompanied by fever and regional lymphadenopathy. In males: herpes progenetialis.
3) **Meningoencephalitis (type 1, 2):** may result from a primary infection of the CNS; however, in some instances, illness follows viral **recurrence** in individuals with pre-existing antibodies.
4) **Keratoconjunctivitis (type 1)**: corneal ulcerations induced by herpesvirus may be quite deep and can result in blindness.
5) **Eczema herpeticum (type 1)**: complication of eczema or sever atopic dermatitis. The abraded weeping and denuded skin is inoculated with virus which spreads widely in the absence of the protective cornified epithelium.
6) **Burn injury:** involvement of abraded and injured skin -- may be quite severe.
7) **Neonatal disease (type 2):** disseminated, visceral and congenital infections…fetus is at risk when mother is shedding virus in birth canal.

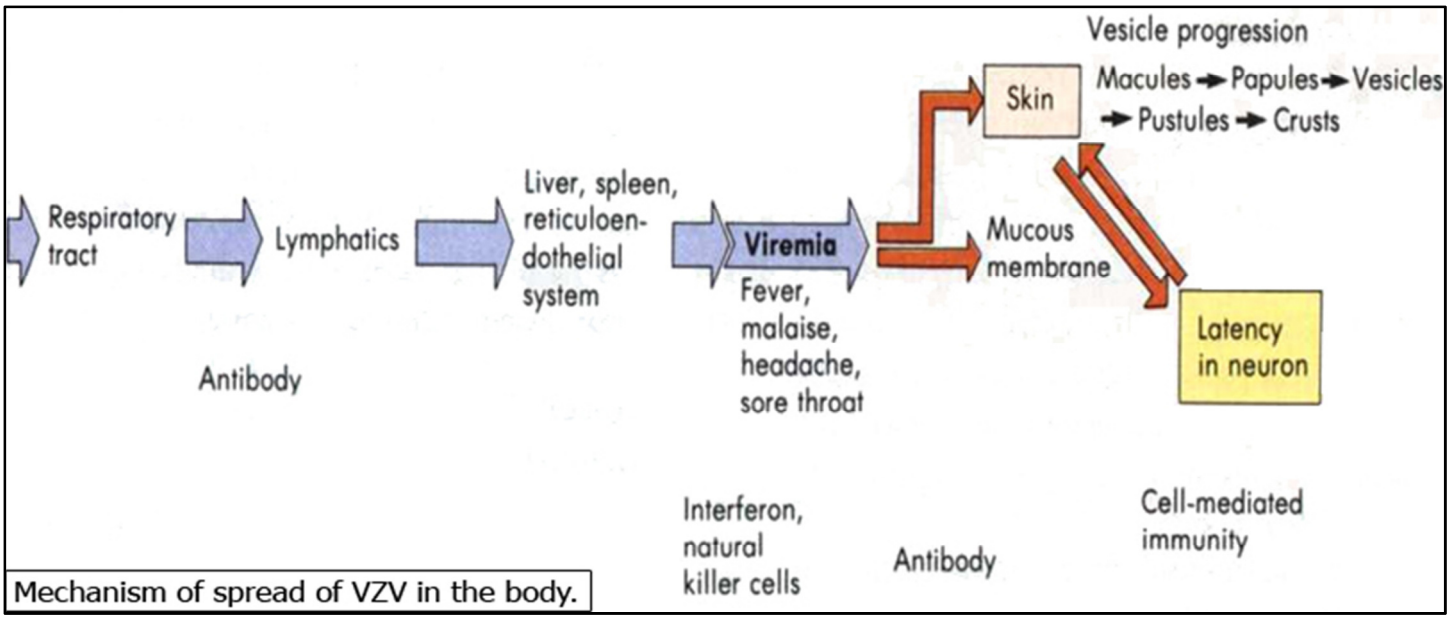
Recurrent Infections:

- Cold sores (herpes labialis)
- Genital lesions (herpes genitalis)
- Keratoconjunctivitis
- Encephalitis
- Meningoencephalitis

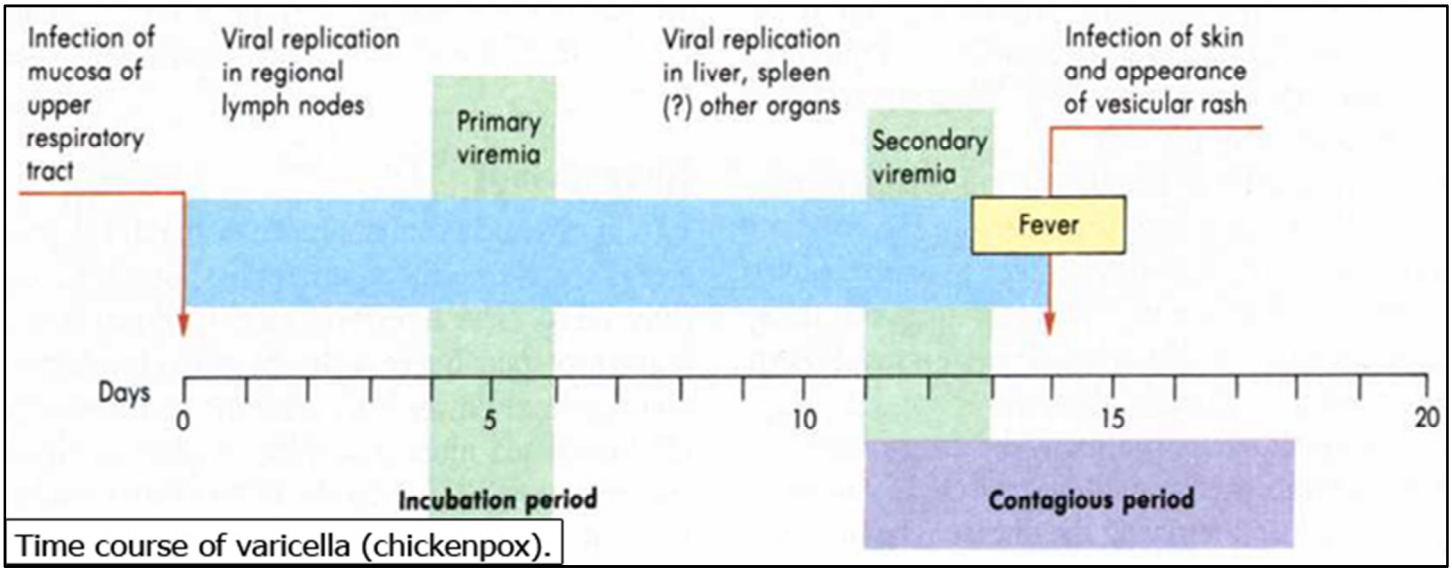
Other Herpes Virus Diseases:

1) **Varicella** (chickenpox): Usually mild disease (except in immunosuppressed) with characteristic rash and pox formation. Begins as respiratory infection then disseminates.
2) **Herpes Zoster** (shingles): Reactivation of latent varicella virus… Formation of painful vesicles unilaterally on the dermatome supplied by the dorsal ganglia…cause of reactivation is immune suppression.
3) **Cytomegaloviruses** (CMV): In adults it causes a mild or subclinical infection. In pregnant women it causes congenital infection like Rubella virus. It is also responsible for a form of mononucleosis which is heterophile **negative**.
4) **Epstein-Barr virus** (EBV): Etiologic agent of infectious mononucleosis (primary target is B-cells) which is heterophile **positive**.

NOTE: Varicella-Zoster is a single virus named by two scientists and it causes both Chickenpox (Varicella) and Shingles (Zoster).



Mechanism of spread of VZV in the body.

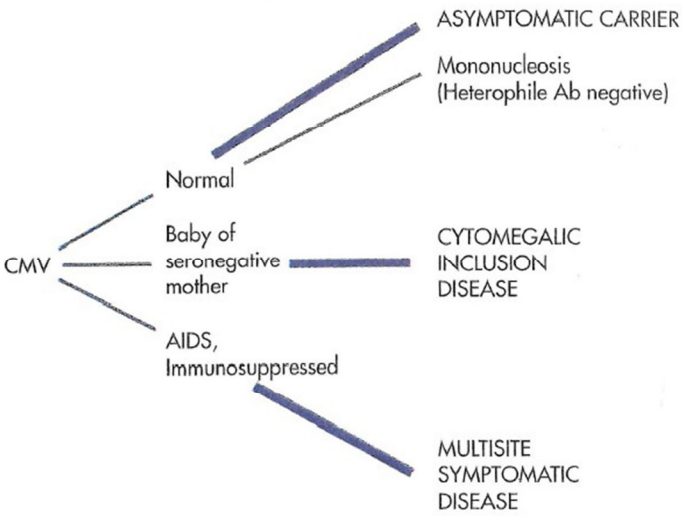


Time course of varicella (chickenpox).

FDA –approved antiviral treatments for herpesvirus infections	
Herpes simplex 1 and 2	**Epstein-Barr virus**
Acyclovir	None
Penciclovir	
Valacyclovir	
Famciclovir	
Adenosine arabinoside	
Iododeoxyuridine	
Trifluridine	
Varicella-Zoster Virus	**Cytomegalovirus**
Acyclovir	Ganciclovir
Famciclovir	Valganciclovir
Valacyclovir	Foscarnet
Varicella-zoster immune globulin	Cidofovir
Zoster immune plasma	
Live vaccine	

The antivirals used for Herpes simplex type 1 & 2 and Varicella-Zoster are not used for Cytomegalovirus because these viruses (HSV-1 & 2 and VZV) contain thymidine kinase enzyme which converts the drugs to their active forms by phosphorylastion while CMV doesn't have this enzyme.

Cytomegalovirus disease



- If it is acquired by direct contact for the first time (primary infection) it is asymptomatic or causes mononucleosis-like disease.
- If it acquired by blood transfusion (post-transfusion syndrome): fever and mononucleosis, FUO (Fever of Unknown Origin), granulomatous hepatitis.
- If a pregnant woman gets this virus during the first trimester this will cause congenital infection (called cytomegalic inclusion disease) which will cause formation of giant cells in the infected organ (*CYTO MEGAL*= giant cell). The clinical picture is similar to Rubella virus infection: petechial rash, hepatosplenomegaly, thrombocytopenia, anemia, CNS damage, low birth weight, mental retardation, partial deafness and eye disease. This disease belongs to the **TORCH** syndrome which stands for **To**xoplasma, **R**ubella, **C**ytomegalovirus and **H**erpes simplex virus. In developed countries there is a test for **TORCH** before marriage to prevent congenital abnormalities.
- If the patient has T-cell impairment, the viral infection will be severe because cellular immunity is an important arm in protection and recovery from viral infections.

CMV Routes of Infection

- Saliva
- Sexual contact
- Transfusion
- Organ transplant (usually renal)

CMV Diagnosis

It is difficult to diagnose CMV depending on clinical data alone. We have to do viral isolation by taking a specimen and inoculating it into a tissue culture in the lab so that we can get a cytopathic effect in a week or two. We usually use the human fibroblastic cells as a tissue culture (spindle-shaped cells). When they become infected with CMV they become rounded (ballooned). We can also use serology by indirect immunofluorescence, cytology on concentrated urine.

CMV Treatment

In AIDS patients we have to treat the disease because in immunocompromised patients the infection may be very severe. We may have retinitis, pneumonitis, and hepatitis. We can use *cidofovir and ganciclovir.* Until now there is no vaccine against this virus.

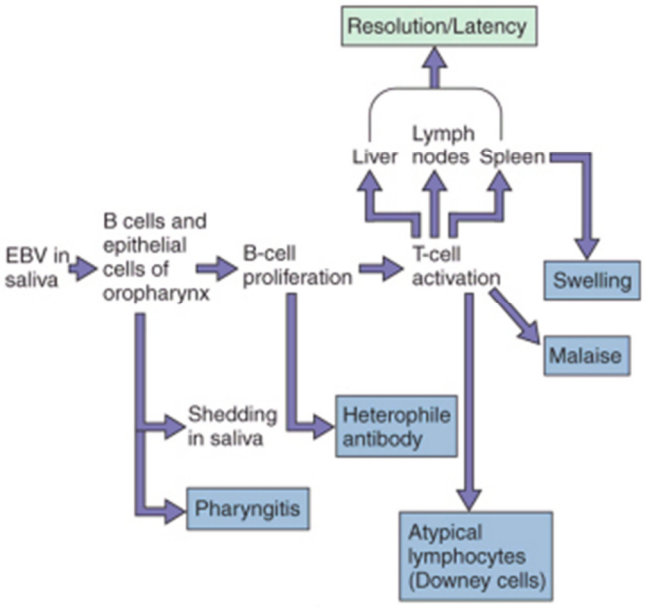
Epstein - Barr virus

- EBV is a herpesvirus first seen by electron microscopy of neoplastic cells from a Burkitt's lymphoma (BL) in 1964.
- Antibody to EBV is found in sera of almost all patients with BL or nasopharyngeal carcinoma.
- Antibody to EBV was found in 80% of low-income adults in Philadelphia and 100% of adults in developing countries; most didn't have BL.
- EBV usually results in infectious mononucleosis (IM) in North America and BL in Africa and other parts of the world. It is also associated with nasopharyngeal carcinoma.

EBV Disease Characteristics

- EBV can be cultured in normal human B lymphocytes (virus attaches to complement C3b receptor) which then begin to behave like neoplastic lymphoma cells. These cells undergo blastogenesis and begin secreting vast amounts of polyclonal (heterophile) immunoglobulins.
- Infection is followed by the prompt appearance of cytotoxic T cells which proceed to turn off activated B cells (the "atypical lymphocytes" are the T cells).
- ***Paul-Bunnell test:*** Heterophil Ab (IgM antibodies which agglutinate sheep and horse RBCs) appears in 80% of patients with Infectious Mononucleosis. These antibodies appear approximately four weeks after onset of symptoms, but are not EBV specific antibodies.

Pathogenesis of EBV



Diagnostic Procedures For Herpesviruses

1) **Cell Culture:** Cell rounding > fusion > giant cell formation (HSV)
2) **Immunofluorescence**: Intense nuclear staining for all herpesviruses
3) **ELISA and Western Blot:** Specificity based on glycoprotein
4) **PCR**
5) **TORCH:** Serologic assay