Medical Virology for 2nd Year M.D. Students

Parvoviruses and Herpesviruses

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Introduction

The reference for the my exam questions: Carroll, Karen C. *et al.* 2016. Jawetz, Melnick & Adelberg's Medical Microbiology

PLUS the topics mentioned during the lectures

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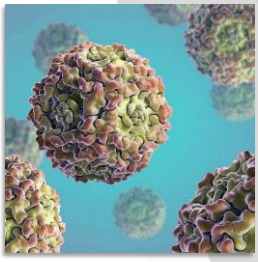
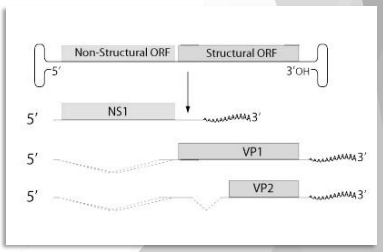
Parvoviruses

- The simplest DNA animal viruses.
- Its replication is dependent on replicating host cells or by co-infecting helper viruses.
- Virions are extremely resistant to inactivation (stable between a pH of 3 and 9 and withstand heating at 56°C for 60 minutes). Virions contain two coat proteins that are encoded by an overlapping, in-frame DNA sequence, so that VP2 is identical in sequence to the carboxy portion of VP1. The major capsid protein, VP2, represents about 90% of virion protein.
- Autonomous parvoviruses usually encapsidate primarily DNA strands complementary to viral mRNA.





Important Properties of Parvoviruses

Virion: Icosahedral, 18–26 nm in diameter, 32 capsomeres

Composition: DNA (20%), protein (80%)

Genome: Single-stranded DNA, linear, 5.6 kb, MW 1.5–2.0 million

Proteins: One major (VP2) and one minor (VP1)

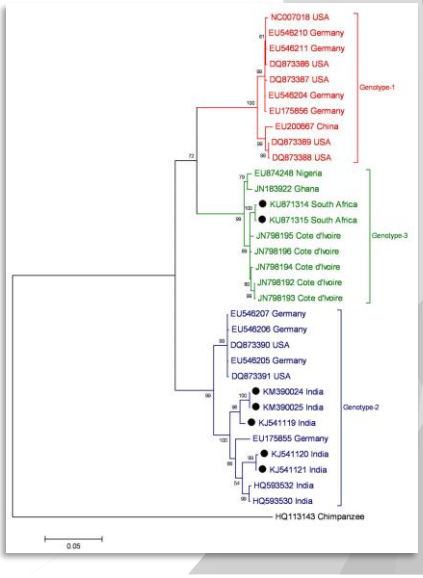
Envelope: None

Replication: Nucleus, dependent on functions of dividing host cells

Outstanding characteristics:
Very simple viruses
Human pathogen, B19, has tropism for red blood cell progenitors
One genus contains viruses that are replication-defective and require a helper virus

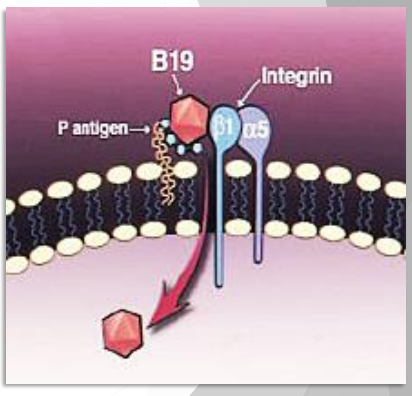
Classification of Parvoviruses

- Subfamilies of *Parvoviridae*: *Parvovirinae* (infect vertebrates and *Densovirinae* (infect insects).
- *Parvovirinae* comprise five genera. Parvovirus B19 is the most common member of the *Erythrovirus* genus. There are three human genotypes in this genus.
- The three human bocaviruses are in the *Bocavirus* genus.
- The genus *Dependovirus* contains members that are defective and depend on a helper virus (an adenovirus or herpesvirus) for replication.
- Human "adeno-associated viruses" have not been linked with any disease.



Parvovirus Replication

- It is difficult to culture human B19 parvovirus; only primary erythroid progenitors are known to be permissive for B19 infection.
- **The cellular receptor for B19 is blood group P antigen (globoside)**. P antigen is expressed on mature erythrocytes, erythroid progenitors, and fetal liver and heart, which helps explain the narrow tissue tropism of B19 virus. **The α5β1 integrin is believed to be a co-receptor for B19 entry**.
- **Viral DNA replication occurs in the nucleus**. They must infect dividing cells with cellular DNA polymerases are involved. The non-structural protein, NS1, is required for virus replication. Viral replication results in cell death.

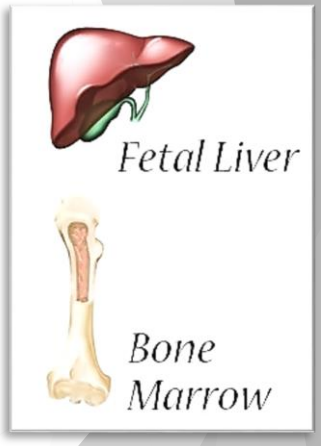


Human Diseases Associated with B19 Parvovirus

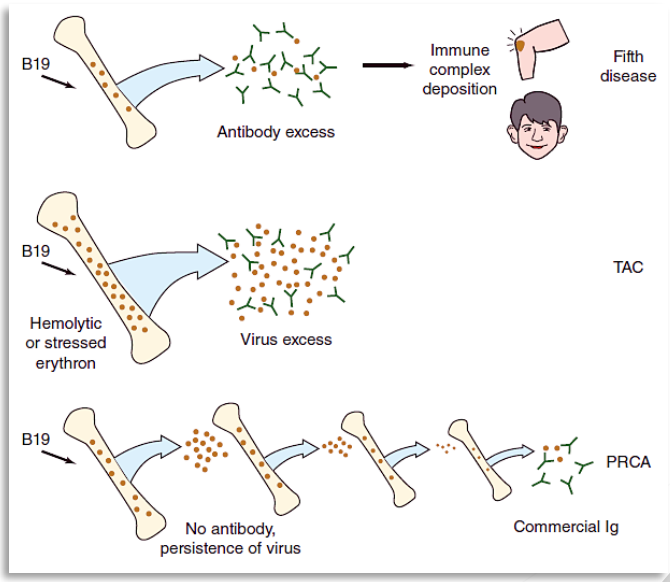
Syndrome	Host or Condition	Clinical Features
Erythema infectiosum	Children (fifth disease) Adults	Cutaneous rash Arthralgia-arthritis
Transient aplastic crisis	Underlying hemolysis	Severe acute anemia
Pure red cell aplasia	Immunodeficiencies	Chronic anemia
Hydrops fetalis	Fetus	Fatal anemia

Parvovirus Infections in Humans

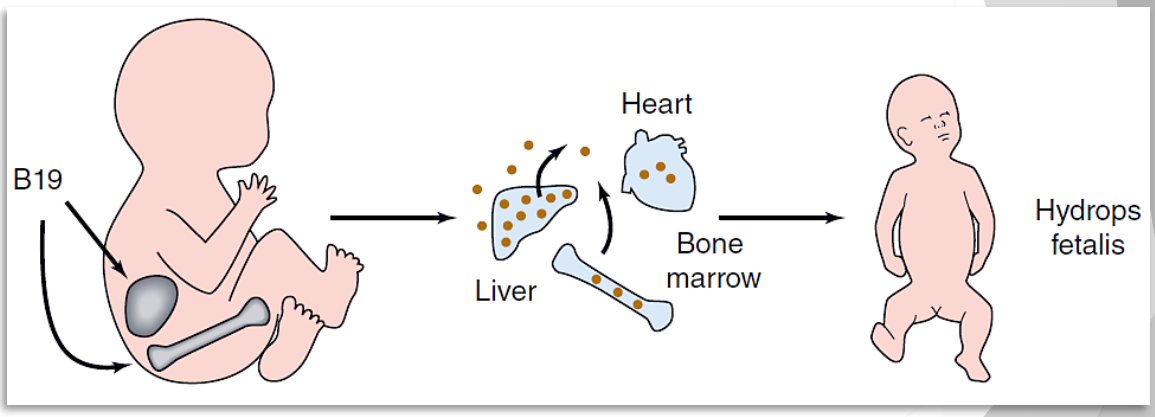
- Immature cells in the erythroid lineage are targets for B19 parvovirus infection.
- The major sites of B19 virus replication in patients are **adult marrow**, and the **fetal liver**.
- Viral replication causes cell death, interrupting red blood cell production.
- In immunocompromised patients, persistent B19 infections occur, resulting in chronic anemia. In cases of fetal death, chronic infections may have caused severe anemia in the fetus.



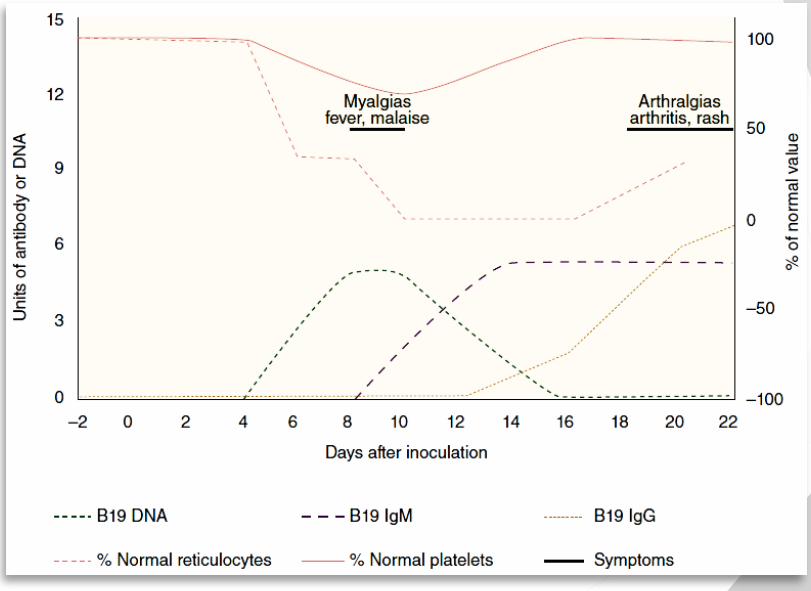
Pathogenesis of B19 Parvovirus Diseases



Pathogenesis of B19 Parvovirus Diseases



Clinical and laboratory findings of B19 infection in adult volunteers

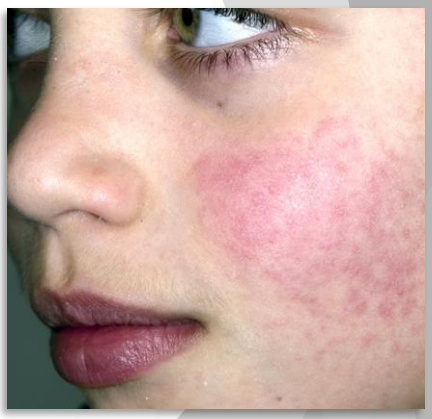


Parvovirus B19 Infections in Humans

- Persistent infections occur in patients with immune deficiencies resulting in anemia.
- The rash associated with erythema infectiousm is at least partly immune complex-mediated.
- **Transmission is by the respiratory route**. There is no evidence of virus excretion in feces or urine.
- The virus can also be transmitted parenterally by transfusion and vertically.
- The pathogenesis of human bocavirus infection is not yet known. Because it has been found in respiratory specimens, it is presumed to infect the respiratory tract and be transmitted by the respiratory route. It has also been detected in stool and serum samples.

Clinical Findings
Erythema Infectiosum (Fifth Disease)

- The most common manifestation of B19 infection.
- It is most common in children of early school age and occasionally affects adults, both in sporadic and epidemic forms.
- Mild constitutional symptoms may accompany the rash, which has a typical **"slapped cheek" appearance**.
- **Joint involvement is a prominent feature in adult cases**; joints in the hands and the knees are most frequently affected. The symptoms mimic rheumatoid arthritis, and the arthropathy may persist for weeks, months, or years.



Clinical Findings
Erythema Infectiosum (Fifth Disease)

- The incubation period is usually 1–2 weeks but may extend to 3 weeks.
- Viremia occurs 1 week after infection and persists for about 5 days with the upper respiratory as the site of viral shedding.
- The first phase of illness at the end of the first week include fever, malaise, myalgia, chills, and itching coinciding with viremia and reticulocytopenia and with detection of circulating IgM–parvovirus immune complexes.
- After an incubation period of about 17 days, a second phase of illness begins. The appearance of an erythematous facial rash and a lacelike rash on the limbs or trunk may be accompanied by joint symptoms, especially in adults. The illness is short-lived, with the rash fading after 2–4 days, although the joint symptoms may persist longer. Specific IgG antibodies appear about 15 days post-infection.

Clinical Findings
Transient Aplastic Crisis and Pure Red Cell Aplasia

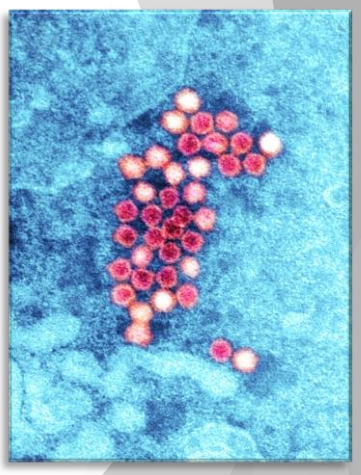
- Parvovirus B19 is the cause of transient aplastic crisis that may complicate chronic hemolytic anemia, such as in patients with SCD, thalassemias, and AHA in adults or may occur after BMT with absence of erythroid precursors in the marrow, accompanied by a rapid worsening of anemia.
- The temporary arrest of production of red blood cells becomes apparent only in patients with chronic hemolytic anemia because of the short life span of their erythrocytes.
- Symptoms of transient aplastic crisis occur during the viremic phase of infection.
- Persistent infections will cause chronic suppression of BM and chronic severe anemia in immunocompromised patients (congenital immunodeficiency, malignancies, AIDS, and organ transplants), which is called pure red cell aplasia.

B19 Parvovirus Infection During Pregnancy

- Maternal infection with B19 virus may result in hydrops fetalis and fetal death due to severe anemia.
- Fetal death occurs most commonly before the 20th week of pregnancy.
- Maternal–fetal transmission may occur most commonly in pregnant women with high plasma viral loads.

Human Bocavirus Respiratory and GI Infections

- Human bocavirus has been detected in 1.5% to 11.3% of respiratory tract samples from young children with respiratory infections.
- It is prevalent among children with acute wheezing.
- The virus has been detected in about 3% of stool samples from children with acute gastroenteritis.
- Co-infection rates with other enteric pathogens were high, so any causative role of bocavirus in gastroenteritis is unknown.



Laboratory Diagnosis of Parvovirus Infections

- The most sensitive tests detect viral DNA.
- Available tests are PCR, probe hybridization of serum or tissue extracts, and in situ hybridization of fixed tissue. **PCR is the most sensitive assay**.
- B19 DNA has been detected in serum, blood cells, tissue samples, and respiratory secretions. During acute infections, viral loads in the blood can reach approximately 10^{11} genome copies/mL.
- The only assay currently available for human bocavirus is PCR. Bocavirus DNA has been found in serum, saliva, stool samples, and respiratory specimens.

Laboratory Diagnosis of Parvovirus Infections

- Serologic assays based on recombinant parvovirus B19 antigens are used to measure antibodies. VP2 virus-like particles appear to be optimal as antigen for antibody detection. Detection of B19 IgM antibody is indicative of recent infection; it is present for 2–3 months after infection.
- B19 IgG antibody against conformational epitopes on VP1 and VP2 persists for years, although antibody responses against linear epitopes decline within months post-infection. Antibody may not be found in immunodeficient patients with chronic B19 infections. In those patients, chronic infection is diagnosed by detecting viral DNA.
- Antigen detection assays can identify high-titered B19 virus in clinical samples. Immunohistochemistry has been used to detect B19 antigens in fetal tissues and bone marrow.
- B19 and bocaviruses are difficult to grow. Virus isolation is not used to detect infection.

Epidemiology of Parvovirus Infections

- The B19 virus is widespread. Infections can occur throughout the year in all age groups.
- Up to 60% of all adults and 90% of elderly people are seropositive.
- B19 infection is transmitted via the respiratory tract. Transfer among siblings and children in schools and daycare centers is the main path of transmission.
- Many infections are subclinical.
- Whereas patients with aplastic crisis are likely to be infectious during the course of their illness, patients with fifth disease are probably no longer infectious by the time of onset of rash.
- The epidemiology of human bocavirus is not known. It has been found in young children and appears to be global in distribution.

Treatment, Prevention and Control of Parvovirus Infections

- Fifth disease and transient aplastic crisis are treated symptomatically. The latter may require transfusion therapy.
- Commercial immunoglobulin preparations contain neutralizing antibodies to human parvovirus. They can sometimes ameliorate persistent B19 infections in immunocompromised patients and in those with anemia.
- There is no treatment for human bocavirus infections.
- There is no vaccine against human parvovirus.
- There is no antiviral drug therapy.

Herpesviruses

- Herpesviruses are important viral pathogens with a wide spectrum of diseases
- They are able to establish **lifelong persistent infections** in their hosts and to undergo **periodic reactivation** (clinically similar or different from the disease caused by the primary infection) with serious health complications in case of reactivation in immunosuppressed patients.
- Herpesviruses possess a large number of genes, some of which with protein products making them susceptible to antiviral chemotherapy.
- The herpesviruses that commonly infect humans include HSV-1, HSV-2, VZV, CMV, EBV, herpesviruses 6 and 7, and KSHV. Herpes B virus of monkeys can also infect humans. There are nearly 100 viruses of the herpes group that infect many different animal species.

Important Properties of Herpesviruses

Virion: Spherical, 150–200 nm in diameter (icosahedral)

Genome: Double-stranded DNA, linear, 125–240 kbp, reiterated sequences

Proteins: More than 35 proteins in virion

Envelope: Contains viral glycoproteins, Fc receptors

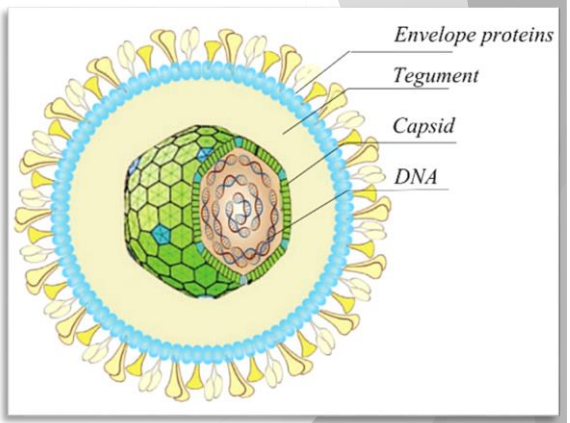
Replication: Nucleus, bud from nuclear membrane

Outstanding characteristics:

- Encode many enzymes
- Establish latent infections
- Persist indefinitely in infected hosts
- Frequently reactivated in immunosuppressed hosts
- Some cause cancer

Structure and Composition of Herpesviruses

- Herpesviruses share architectural details and are indistinguishable by EM.
- All herpesviruses have a core of ds-DNA (125–240 kbp) that is linear, surrounded by capsid of icosahedral symmetry with 162 capsomeres. The envelope is derived from **the nuclear membrane** and contains viral gp spikes about 8 nm long.
- An amorphous, sometimes asymmetric structure between the capsid and envelope is designated the **tegument**.
- The enveloped form measures 150–200 nm; the "naked" virion, 125 nm.



Structure and Composition of Herpesviruses

- Treatment with restriction endonucleases yields characteristically different cleavage patterns for herpesviruses and even for different strains of each type. This "fingerprinting" of strains allows epidemiologic tracing of a given strain.
- Herpesvirus genome is large and encodes at least 100 different proteins. Of these, more than 35 polypeptides are involved in the structure of the virus particle; at least 10 are part of the viral envelope.
- Herpesviruses encode an array of virus-specific enzymes involved in nucleic acid metabolism, DNA synthesis, gene expression, and protein regulation (DNA polymerase, helicase-primase, thymidine kinase, transcription factors, protein kinases).
- Many herpesvirus genes appear to be viral homologs of cellular genes.

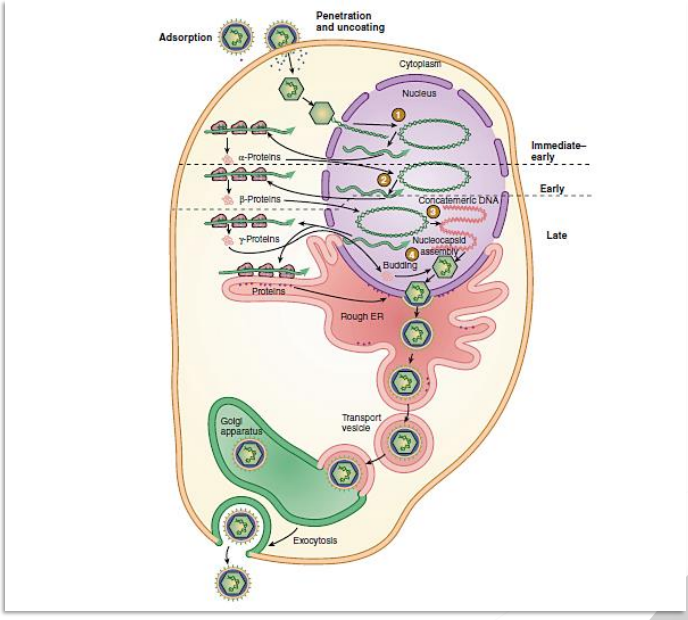
Classification of Herpesviruses

- Division into subfamilies is based on biologic properties of herpesviruses.
- Alphaherpesviruses are fast-growing, cytolytic viruses that tend to establish latent infections in neurons.
- Betaherpesviruses are slow growing and may be cytomegalic and become latent in secretory glands and kidneys.
- Gammaherpesviruses, exemplified by EBV (genus Lymphocryptovirus), infect and become latent in lymphoid cells. KSHV, designated as HHV-8, is classified in the Rhadinovirus genus.
- There is little antigenic relatedness among members of the herpesvirus group. Only HSV-1 and HSV-2 share a significant number of common antigens. HHV-6 and HHV-7 exhibit a few cross-reacting epitopes.

Classification of Herpesviruses

Subfamily ("-herpesvirinae")	Biologic Properties: Growth Cycle and Cytopathology	Biologic Properties: Latent Infections	Genus ("-*virus*")	Examples: Official Name ("Human Herpesvirus")	Examples: Common Name
Alpha	Short, cytolytic	Neurons	*Simplex*	1	Herpes simplex virus type 1
				2	Herpes simplex virus type 2
			Varicello	3	Varicella-zoster virus
Beta	Long, cytomegalic	Glands, kidneys	*Cytomegalo*	5	Cytomegalovirus
	Long, lymphoproliferative	Lymphoid tissue	*Roseolo*	6	Human herpesvirus 6
				7	Human herpesvirus 7
Gamma	Variable, lymphoproliferative	Lymphoid tissue	*Lymphocrypto*	4	Epstein-Barr virus
			Rhadino	8	Kaposi sarcoma-associated herpesvirus

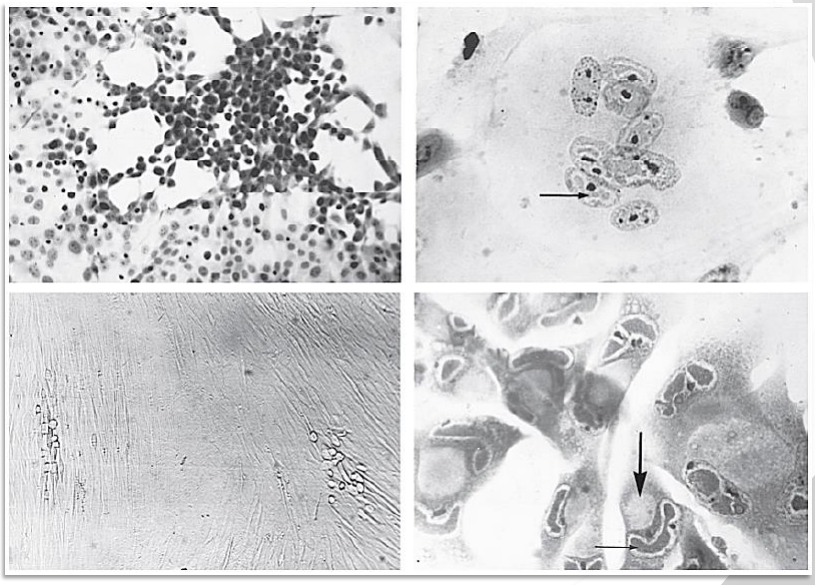
Replication of Herpesviruses



Replication of Herpesviruses

- Several herpesviruses bind to cell surface glycosaminoglycans, principally heparan sulfate. Virus attachment also involves binding to one of several co-receptors (e.g., members of IgSF).
- VP16, a tegument protein, complexes with several cellular proteins and activates initial viral gene expression.
- Viral DNA is transcribed throughout the replicative cycle by cellular RNA polymerase II but with the participation of viral factors.
- Maturation occurs by budding of nucleocapsids through the altered inner nuclear membrane.
- The length of the replication cycle varies from about 18 hours for HSV to more than 70 hours for CMV. Cells productively infected with herpesviruses are invariably killed.

Cytopathic effects induced by herpesviruses



Replication of Herpesviruses

- Herpesviruses have recently been found to express multiple microRNAs, small (~22 nucleotides) single-stranded RNAs that function post-transcriptionally to regulate gene expression.
- It is predicted that these viral microRNAs are important in regulating entry into or exit from (or both) the latent phase of the virus life cycle and may be attractive targets for antiviral therapy.

HERPESVIRUS INFECTIONS IN HUMANS

Herpes Simplex Viruses

- HSVs are widespread in the human population. They establish latent infections in nerve cells; recurrences are common.
- There are two distinct HSV, types 1 and 2 (HSV-1 and HSV-2). The two viruses cross-react serologically, but some unique proteins exist for each type. They differ in their mode of transmission. Whereas HSV-1 is spread by contact, usually involving infected saliva, HSV-2 is transmitted sexually or from a maternal genital infection to a newborn.
- The HSV growth cycle proceeds rapidly, requiring 8–16 hours for completion.
- Among viral late gene products, (gD) is the most potent inducer of neutralizing antibodies. gC is a complement (C3b)-binding protein, and gE is an Fc receptor, binding to the Fc portion of immunoglobulin G (IgG). gG is type specific and allows for antigenic discrimination between HSV-1 (gG-1) and HSV-2 (gG-2).

Comparison of Herpes Simplex Virus Types 1 and 2

Characteristics	HSV-1	HSV-2
Biochemical		
Viral DNA base composition (G + C) (%)	67	69
Buoyant density of DNA (g/cm^3)	1.726	1.728
Buoyant density of virions (g/cm^3)	1.271	1.267
Homology between viral DNAs (%)	~50	~50
Biologic		
Animal vectors or reservoirs	None	None
Site of latency	Trigeminal ganglia	Sacral ganglia
Epidemiologic		
Age of primary infection	Young children	Young adults
Transmission	Contact (often saliva)	Sexual

Comparison of Herpes Simplex Virus Types 1 and 2

Characteristics	HSV-1	HSV-2
Clinical		
Primary infection:		
Gingivostomatitis	+	–
Pharyngotonsillitis	+	–
Keratoconjunctivitis	+	–
Neonatal infections	±	+
Recurrent infection:		
Cold sores, fever blisters	+	–
Keratitis	+	–
Primary or recurrent infection:		
Cutaneous herpes		
Skin above the waist	+	±
Skin below the waist	±	+
Hands or arms	+	+
Herpetic whitlow	+	+
Eczema herpeticum	+	–
Genital herpes	±	+
Herpes encephalitis	+	–
Herpes meningitis	±	+

Pathogenesis and Pathology of Herpes Simplex Viruses

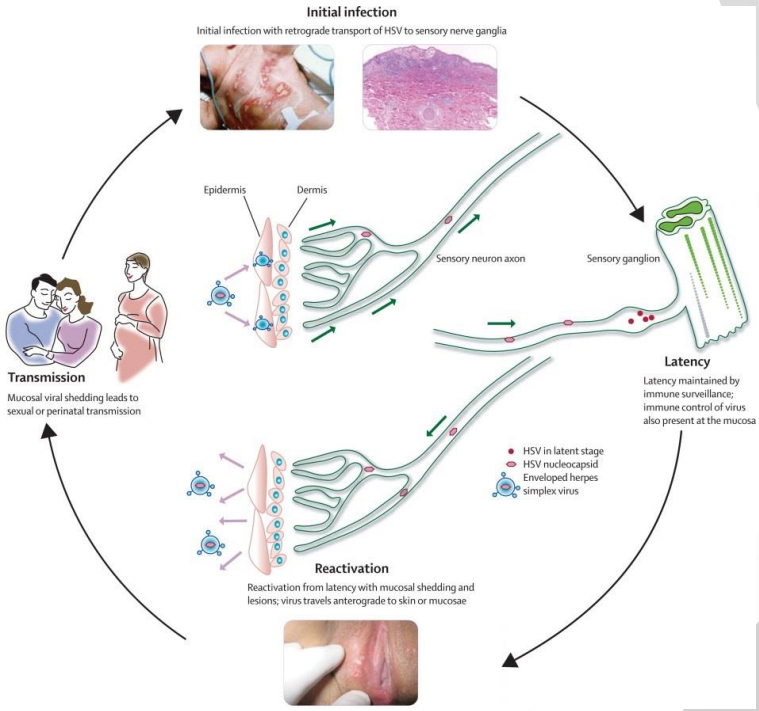
- Pathologic changes are due to necrosis of infected cells with inflammatory response. Lesions induced in the skin and mucous membranes by HSV-1 and HSV-2 are the same and resemble those of VZV. Changes induced by HSV are similar for primary and recurrent infections.
- Characteristic histopathologic changes include ballooning of infected cells, production of Cowdry type A intranuclear inclusion bodies, margination of chromatin, and formation of multinucleated giant cells. Cell fusion provides an efficient method for cell-to-cell spread of HSV, even in the presence of neutralizing antibody.
- In primary infection, HSV must encounter mucosal surfaces or broken skin for an infection to be initiated (unbroken skin is resistant).

Pathogenesis and Pathology of Herpes Simplex Viruses

- HSV-1 infections are spread by direct contact with infected saliva.
- HSV-2 is usually transmitted by genital routes. Viral replication occurs first at the site of infection. Virus then invades local nerve endings and is transported by **retrograde axonal flow to dorsal root ganglia**, where, latency is established. Whereas oropharyngeal HSV-1 infections result in latent infections in the trigeminal ganglia, genital HSV-2 infections lead to latently infected sacral ganglia.
- Viremia is more common during primary HSV-2 infections than during HSV-1 infections.
- Primary HSV infections are mostly asymptomatic or mild. Widespread organ involvement can result when an immunocompromised host is not able to limit viral replication.
- In latent infection, the virus resides in latently infected ganglia in a non-replicating state.

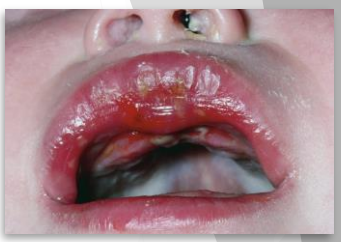
Pathogenesis and Pathology of Herpes Simplex Viruses

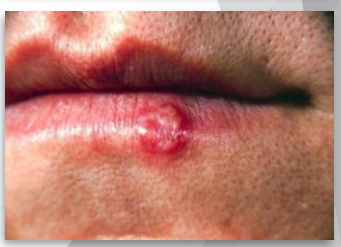
- Provocative stimuli can reactivate virus from the latent state, including axonal injury, fever, physical or emotional stress, and exposure to ultraviolet light. The virus follows axons back to the peripheral site, and replication proceeds at the skin or mucous membranes. Spontaneous reactivations occur despite HSV-specific humoral and cellular immunity in the host. However, this 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. When symptomatic, episodes of recurrent HSV-1 infection are usually manifested as cold sores (fever blisters) near the lip. More than 80% of the human population harbor HSV-1 in a latent form, but only a small portion experience recurrences.



Clinical Findings of Herpes Simplex Viruses

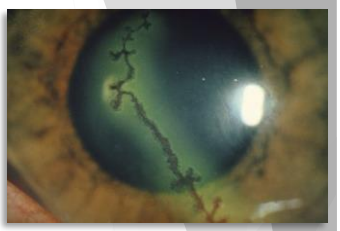
- Primary HSV-1 infections are mostly asymptomatic. The incubation period is short (~3–5 days, range of 2–12 days), clinical illness lasts 2–3 weeks. Symptoms include fever, sore throat, vesicles and ulcers and gingivostomatitis.
- Primary infections in adults commonly cause pharyngitis and tonsillitis. Localized lymphadenopathy may occur.
- Recurrent disease vesicular mostly at the border of the lip. Intense pain occurs at the outset but fades over 4–5 days. Lesions progress through the pustular and crusting stages, and healing without scarring is usually complete in 8–10 days.
- Many recurrences of oral shedding are asymptomatic and of short duration (24 hours).

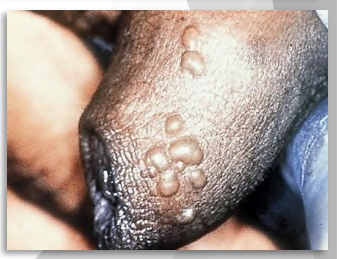




Clinical Findings of Herpes Simplex Viruses

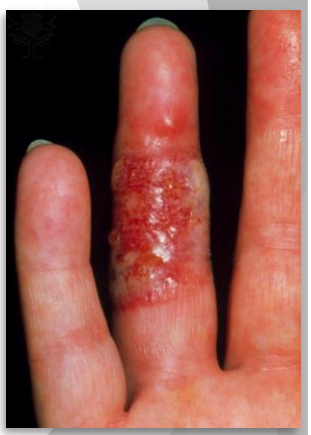
- HSV-1 may cause severe keratoconjunctivitis, which appears as dendritic keratitis or corneal ulcers or as vesicles on the eyelids. Progressive involvement of the corneal stroma, can cause permanent opacification and blindness. HSV-1 infections are the second cause of corneal blindness in the US.
- Genital disease is usually caused by HSV-2, **although HSV-1 can also cause clinical episodes of genital herpes**.
- Primary genital herpes infections can be severe (very painful and associated with fever, dysuria, and inguinal lymphadenopathy). Genital herpes is characterized by vesiculoulcerative lesions of the penis of the male or of the cervix, vulva, vagina, and perineum of the female. Complications include extragenital lesions (~20% of cases) and aseptic meningitis (~10% of cases).





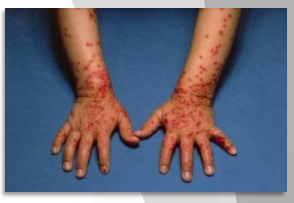
Clinical Findings of Herpes Simplex Viruses

- Recurrences of genital herpes are common and tend to be mild.
- A limited number of vesicles appear and heal in about 10 days. Virus is shed for only a few days.
- Some recurrences are asymptomatic with shedding lasting less than 24 hours. Whether a recurrence is symptomatic or asymptomatic, a person shedding virus can transmit the infection to sexual partners.
- Cutaneous HSV infections are uncommon in healthy persons. WHY?
- Localized lesions caused by HSV-1 or HSV-2 may occur in abrasions contaminated with the virus (e.g. fingers of dentists and hospital personnel (herpetic whitlow) and on the bodies of wrestlers (herpes gladiatorum or mat herpes).



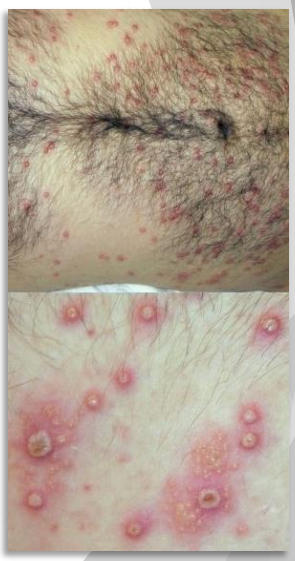
Clinical Findings of Herpes Simplex Viruses

- Eczema herpeticum is a primary infection, usually with HSV-1, in a person with chronic eczema.
- HSV-1 is the most common cause of sporadic, fatal encephalitis in US, with high mortality rate, and those who survive often having residual neurologic defects. About half of patients with HSV encephalitis appear to have primary infections, and the rest appear to have recurrent infection.
- Neonatal herpes occurs in ~ 1 in 5000 deliveries per year.
- The most common route of infection is during birth by contact with herpetic lesions in the birth canal.
- About 75% of neonatal herpes infections are caused by HSV-2.
- The overall mortality rate of untreated disease is 50%.



Clinical Findings of Herpes Simplex Viruses

- Immunocompromised patients are at increased risk of developing 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.



Immunity to Herpes Simplex Viruses

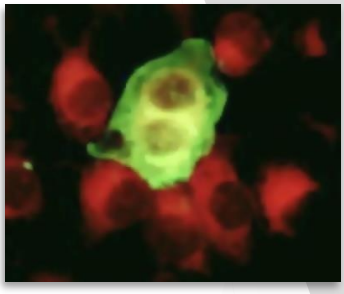
- The period of greatest susceptibility to primary herpes infection occurs between ages 6 months and 2 years. WHY?
- HSV-1 antibodies are present in most persons by adolescence. Antibodies to HSV-2 rise during the age of adolescence and sexual activity.
- Cell-mediated immunity and nonspecific host factors (NK cells, IFNs) are important in controlling both primary and recurrent HSV infections.

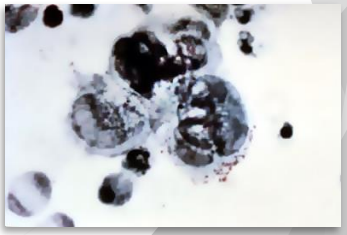
Laboratory Diagnosis of Herpes Simplex Viruses

- PCR is both sensitive and specific (e.g. for CSF infections PCR replaced virus culture).
- **Virus isolation remains the definitive diagnostic approach**. Virus may be isolated during primary infection and during asymptomatic periods. Therefore, the isolation of HSV is not in itself sufficient evidence to indicate that the virus is the causative agent of a disease under investigation.
- HSV is easy to cultivate, and cytopathic effects usually occur in only 2–3 days. The agent is then identified by neutralization test or immunofluorescence staining with specific antiserum.

Laboratory Diagnosis of Herpes Simplex Viruses

- A rapid cytologic method is to stain scrapings obtained from the base of a vesicle (eg, with Giemsa's stain); the presence of multinucleated giant cells indicates that herpesvirus (HSV-1, HSV-2, or varicella-zoster) is present, distinguishing lesions from those caused by coxsackieviruses and non-viral entities.
- Antibodies appear in 4–7 days after infection and reach a peak in 2–4 weeks. Detection methods available include enzyme immunoassays.
- The diagnostic value of serologic assays is limited by the multiple antigens shared by HSV-1 and HSV-2. The use of HSV type-specific antibodies, allows more meaningful serologic tests.



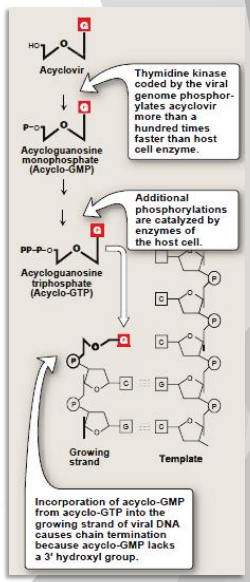


Epidemiology of Herpes Simplex Viruses

- HSVs are distributed worldwide.
- No animal reservoirs or vectors are involved with the human viruses. Transmission is by contact with infected secretions.
- The epidemiology of HSV-1 and HSV-2 differs. The highest incidence of HSV-1 infection occurs among children 6 months to 3 years of age. By adulthood, 70–90% of persons have type 1 antibodies.
- HSV-2 is usually acquired as an STD, so antibodies are seldom found before puberty.
- Studies estimated that transmission of genital herpes in more than 50% of cases resulted from sexual contact in the absence of lesions or symptoms.

Treatment of Herpes Simplex Viruses

- Several antivirals are effective against HSV infections, including acyclovir, valacyclovir, and vidarabine. All are inhibitors of viral DNA synthesis.
- Acyclovir, a nucleoside analog, is monophosphorylated by the **HSV thymidine kinase**. The acyclovir triphosphate is efficiently incorporated into viral DNA by the HSV polymerase, where it then prevents chain elongation.
- The drugs may suppress clinical manifestations, shorten time to healing, and reduce recurrences of genital herpes. However, HSV remains latent in sensory ganglia. Drug-resistant virus strains may emerge.

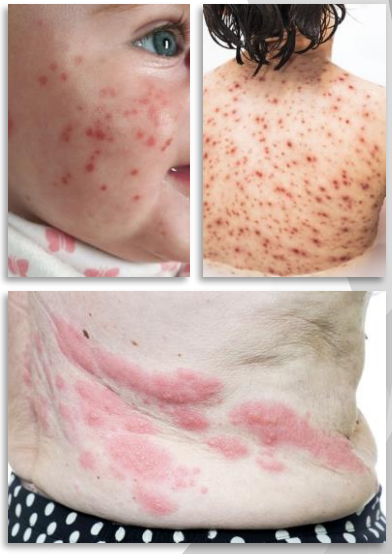


Prevention, and Control of Herpes Simplex Viruses

- Newborns and persons with eczema should be protected from exposure to persons with active herpetic lesions.
- Patients with genital herpes should be counseled that asymptomatic shedding is frequent and that the risk of transmission can be reduced by antiviral therapy and condom usage.
- Experimental vaccines of various types are being developed. One approach is to use purified glycoprotein antigens found in the viral envelope, expressed in a recombinant system. Such vaccines might be helpful for the prevention of primary infections. A promising recombinant HSV-2 glycoprotein vaccine failed to prevent herpesvirus infections in a large clinical trial in 2010.

Varicella Zoster Virus (VZV)

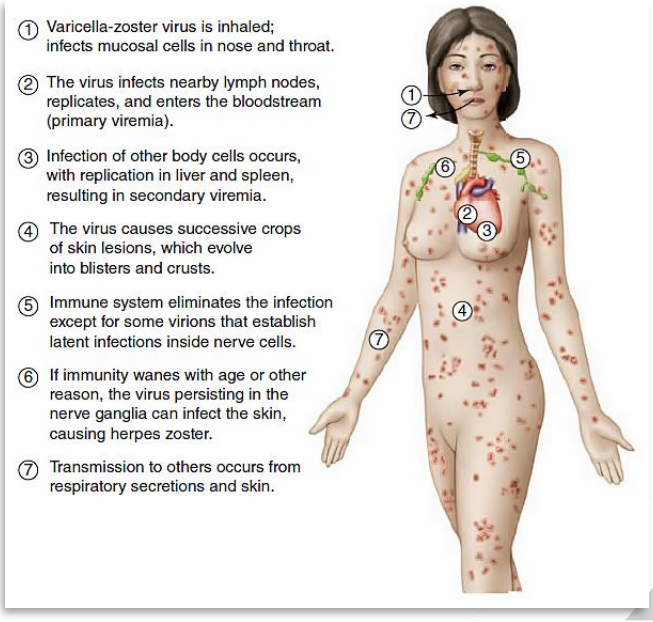
- **Varicella** (chickenpox) is a mild, highly contagious disease, chiefly of children, characterized clinically by a generalized vesicular eruption of the skin and mucous membranes. The disease may be severe in adults and in immunocompromised individuals.
- **Zoster** (shingles) is a sporadic, incapacitating disease of elderly or immunocompromised individuals that is characterized by pain and a rash limited in distribution to the skin innervated by a single sensory ganglion. The lesions are similar to those of varicella.



Varicella Zoster Virus (VZV)

- Both diseases are caused by the same virus. Whereas varicella is the acute disease that follows primary contact with the virus, **zoster is the response of the partially immune host to reactivation of varicella virus present in latent form in neurons in sensory ganglia**.
- Varicella-zoster virus is morphologically identical to HSV.
- It has no animal reservoir.
- Viral isolates from the vesicles of chickenpox or zoster patients exhibit no significant genetic variation. Inoculation of zoster vesicle fluid into children produces chickenpox.

Pathogenesis of primary infection with VZV



Pathogenesis and Pathology of VZV Infection

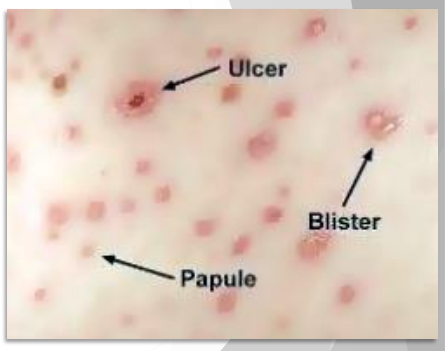
- The route of infection is the mucosa of the upper respiratory tract or the conjunctiva.
- VZV replication and spread are limited by host humoral and cellular immune responses.
- Interferon is likely involved also.
- It has been shown that a VZV-encoded protein, ORF61, antagonizes the β-interferon pathway. This presumably contributes to the pathogenesis of viral infection.

Pathogenesis and Pathology of VZV Infection

- The skin lesions of zoster are histopathologically identical to those of varicella.
- The distribution of lesions in the skin corresponds closely to the areas of innervation from an individual dorsal root ganglion.
- It is believed that waning immunity allows viral replication to occur in a ganglion, causing intense inflammation and pain. Virus travels down the nerve to the skin and induces vesicle formation.
- Cell-mediated immunity is probably the most important host defense in containment of varicella-zoster virus.

Varicella (Chickenpox)

- Subclinical varicella is unusual.
- The incubation period of the disease is 10–21 days.
- Malaise and fever are the earliest symptoms, soon followed by the rash, first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa in the mouth.
- Successive fresh vesicles appear in crops, so that all stages of macules, papules, vesicles, and crusts may be seen at one time.
- The rash lasts about 5 days, and most children develop several hundred skin lesions.

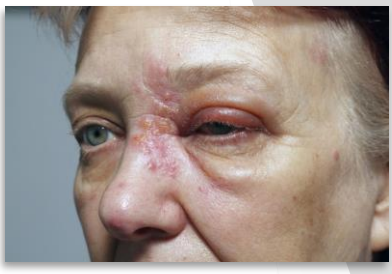


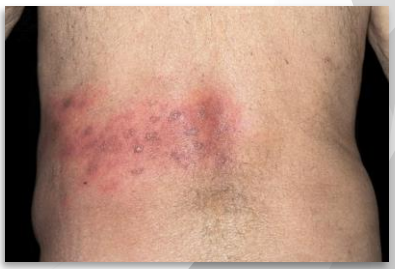
Varicella (Chickenpox)

- Complications are rare in normal children, and the mortality rate is very low.
- Encephalitis does occur in rare cases and can be life threatening.
- Survivors of varicella encephalitis may be left with permanent sequelae.
- In neonatal varicella, the infection is contracted from the mother just before or after birth but without sufficient immune response to modify the disease, which can be fatal.
- Varicella pneumonia is rare in healthy children but is the most common complication in neonates, adults, and immunocompromised patients. It is responsible for many varicella-related deaths.

Zoster (Shingles)

- Zoster usually occurs in persons immunocompromised (e.g. aging), but it develops in healthy young adults.
- It starts with severe pain in the area of skin or mucosa. 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, with the ophthalmic division of the trigeminal nerve involved in 10–15% of cases. The most common complication is postherpetic neuralgia (protracted pain that may continue for months).





Immunity to VZV

- Varicella and zoster are the result of differing host responses.
- Previous infection with varicella can confer lifelong immunity to varicella.
- Antibodies induced by varicella vaccine persist for at least 20 years. Zoster occurs in the presence of neutralizing antibody to varicella.
- The development of varicella-zoster virus-specific cell-mediated immunity is important in recovery from both varicella and zoster. Appearance of local interferon may also contribute to recovery.
- VZV encodes means of evading host immune responses. It downregulates MHC class I and II antigen expression and the β-interferon pathway.

Laboratory Diagnosis of VZV Infection

- VZV DNA can be detected by PCR in saliva, vesicle fluid, skin scrapings, and biopsy material.
- In stained smears of scrapings or swabs of the base of vesicles (Tzanck smear), multinucleated giant cells are seen. These are absent in non-herpetic vesicles.
- Intracellular viral antigens can be demonstrated by immunofluorescence staining of similar smears.
- Virus can be isolated from vesicle fluid early in the course of illness using cultures of human cells in 3–7 days. VZV in vesicle fluid is very labile, and cell cultures should be inoculated promptly.
- Serologic diagnosis can be used as well.

Epidemiology of VZV Infection

- Varicella and zoster occur worldwide. It is highly communicable and is a common epidemic disease of childhood. Adult cases do occur. It is much more common in winter and spring than in summer in temperate climates.
- Zoster occurs sporadically, chiefly in adults and without seasonal prevalence. About 10–20% of adults will experience at least one zoster attack during their lifetime, usually after the age of 50 years.
- A live attenuated varicella vaccine is available. Since the vaccine was introduced in 1995, there has been a steady decline in the incidence of varicella diseases; however, varicella outbreaks continue to occur among school children. WHY?
- Varicella spreads by airborne droplets and by direct contact. A varicella patient is infectious from shortly before the appearance of rash to the first few days of rash.

Treatment of VZV Infection

- Varicella in normal children requires no treatment.
- Neonates and immunocompromised patients with severe infections should be treated.
- Several antiviral compounds provide effective therapy for varicella, including acyclovir, valacyclovir, famciclovir, and foscarnet.
- 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.

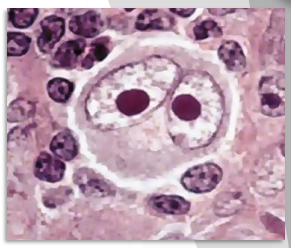
Prevention and Control of VZV Infection

- A single dose of the live attenuated varicella vaccine is highly effective at inducing protection from varicella in children (80–85% effective) but less so in adults (70%).
- The vaccine is about 95% effective in preventing severe disease.
- In 2006, two doses of the vaccine were recommended for children, and that schedule is reportedly more than 98% effective in preventing varicella disease.
- The duration of protective immunity induced by the vaccine is unknown but is probably long term.
- A zoster (shingles) vaccine was licensed in the United States in 2006. It is a 14 times more potent version of the varicella vaccine. The zoster vaccine is recommended for those with chronic medical conditions and for persons older than 60 years of age.

Cytomegalovirus (CMV)

- CMVs are the agents of the most common congenital infection. Cytomegalic inclusion disease is a generalized infection of infants caused by intrauterine or early postnatal infection with the CMVs.
- Inapparent infection is common during childhood and adolescence. Severe CMV infections are frequently found in adults who are immunosuppressed.
- CMV has the largest genetic content of the human herpesviruses. One of its proteins, a cell surface glycoprotein, acts as an Fc receptor that can non-specifically bind the Fc portion of immunoglobulins. This may help infected cells evade immune elimination by providing a protective coating of irrelevant host immunoglobulins.
- Many genetically different strains of CMV are circulating in the human population.

Pathology and Pathogenesis of CMV



- CMV produces a characteristic cytopathic effect: Perinuclear cytoplasmic inclusions form in addition to the intranuclear inclusions typical of herpesviruses. Multinucleated cells are seen. Many affected cells become greatly enlarged.
- CMV may be transmitted from person to person via close contact with virus-bearing material. There is a 4-8 week incubation period.
- The virus causes a systemic infection; it has been isolated from lung, liver, esophagus, colon, kidneys, monocytes, and T and B lymphocytes. The disease is an infectious mononucleosis-like syndrome, although most CMV infections are subclinical.

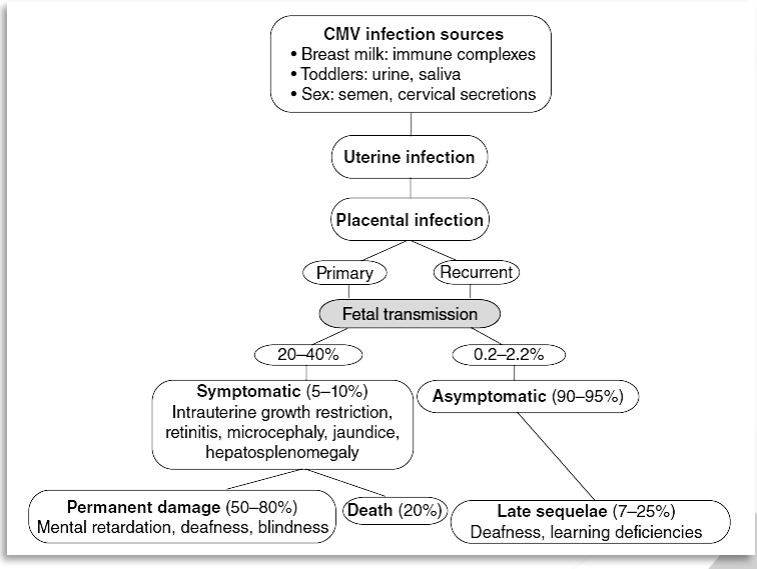
Pathology and Pathogenesis of CMV

- CMV can be shed intermittently from the pharynx and in the urine for months to years after primary infection.
- Cell-mediated immunity is depressed with primary infections, which contributes to the persistence of viral infection. It takes several months for cellular responses to recover.
- Primary CMV infections in immunosuppressed hosts are more severe. Individuals at greatest risk for CMV disease are those receiving organ transplants, those on chemotherapy, and those with AIDS. Infection becomes disseminated.
- **Pneumonia is the most common complication.**
- The host immune response presumably maintains CMV in a latent state in seropositive individuals.

Pathology and Pathogenesis of CMV

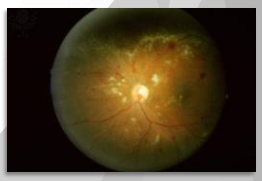
- Congenital infection may be severe. About 1% of live births annually in the US have congenital CMV infections.
- A high percentage of babies with this disease will exhibit developmental defects and mental retardation.
- Generalized cytomegalic inclusion disease results most often from primary maternal infections.
- Whether CMV is acquired in utero or perinatally, a more chronic infection results—with respect to viral excretion—than when the virus is acquired later in life.

Congenital CMV Infection



Clinical Findings of CMV Infection

- Primary CMV infection is usually asymptomatic but occasionally causes a spontaneous infectious mononucleosis syndrome. CMV is estimated to cause 20–50% of heterophil-negative (non-EBV) mononucleosis cases.
- CMV mononucleosis is a mild disease, and complications are rare. Subclinical hepatitis is common.
- Both morbidity and mortality rates are increased with primary and recurrent CMV infections in immunocompromised individuals. Pneumonia is a frequent complication.
- CMV often causes disseminated disease in untreated AIDS patients; gastroenteritis and chorioretinitis are common problems, the latter often leading to progressive blindness.



Clinical Findings of CMV Infection

- Congenital infection may result in death of the fetus in utero. Cytomegalic inclusion disease of newborns is characterized intrauterine growth retardation, jaundice, hepatosplenomegaly, thrombocytopenia, microcephaly, and retinitis.
- Mortality rates are about 20%. The majority of survivors develop significant CNS defects within 2 years; severe hearing loss, ocular abnormalities, and mental retardation are common. About 10% of infants with subclinical congenital CMV infection develop deafness.

Laboratory Diagnosis of CMV Infection

- PCR replaced virus isolation for routine detection of CMV infections. The PCR assays are designed to detect replicating virus, not latent viral genomes. Blood and urine are most commonly tested.
- PCR can provide viral load data, which appears to be important in predicting CMV disease.
- Human fibroblasts are used for virus isolation from throat washings and urine. In cultures, 2–3 weeks are usually needed for the appearance of cytologic changes.
- Serologic detection of IgM suggests a current infection. Serologic assays are not informative for immunocompromised patients.

Epidemiology of CMV Infection

- CMV is present throughout the year, with no seasonal variation.
- The prevalence of infection varies with socioeconomic status, living conditions, and hygienic practices.
- New infections are almost always asymptomatic. After infection, virus is shed from multiple sites. Viral shedding may continue for years, often intermittently, as latent virus becomes reactivated. Thus, exposures to CMV are widespread and common.
- Humans are the only known host for CMV. Transmission requires close person-to-person contact. Virus may be shed in urine, saliva, semen, breast milk, and cervical secretions and is carried in circulating white blood cells. Oral and respiratory spread are probably the dominant routes of CMV transmission. CMV can be transmitted by blood transfusion.

Treatment and Control of CMV Infection

- Ganciclovir has been used successfully to treat life-threatening CMV infections in immunosuppressed patients.
- Ganciclovir also controls progressive hearing loss in neonates with congenital infections.
- Foscarnet, an analog of inorganic pyrophosphate, is recommended for treatment of CMV retinitis. Acyclovir and valacyclovir have shown some benefits in bone marrow and renal transplant patients.
- Screening of transplant donors and recipients for CMV antibody may prevent some transmissions of primary CMV.
- The use of blood from seronegative donors has been recommended when infants will require multiple transfusions.

Epstein Barr Virus (EBV)

- EBV is the causative agent of acute infectious mononucleosis and is associated with nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin and non-Hodgkin lymphomas, and gastric carcinoma.
- The major target cell for EBV is the B lymphocyte. When human B lymphocytes are infected with EBV, continuous cell lines can be established, indicating that cells have been immortalized by the virus.
- EBV initiates infection of B cells by binding to the viral receptor, which is the receptor for the C3d component of complement (CR2 or CD21). EBV directly enters a latent state in the lymphocyte without undergoing a period of complete viral replication. Several patterns of latent viral gene expression are recognized based on the spectrum of proteins and transcripts expressed. These include EBV nuclear antigens (EBNA1, 2, 3A-3C, LP), latent membrane proteins (LMP1, 2), and small untranslated RNAs (EBERs).

Epstein Barr Virus (EBV)

- EBV antigens are divided into three classes based on the phase of the viral life cycle in which they are expressed:
- (1) Latent phase antigens are synthesized by latently infected cells. These include the **EBNAs** and the **LMPs**. Their expression reveals that an EBV genome is present. **Only EBNA1, needed to maintain the viral DNA episomes, is invariably expressed**; expression of the other latent phase antigens may be regulated in different cells. LMP1 mimics an activated growth factor receptor.
- (2) Early antigens are non-structural proteins whose synthesis is not dependent on viral DNA replication. The expression of early antigens indicates the onset of productive viral replication.
- (3) Late antigens are the structural components of the viral capsid (viral capsid antigen) and viral envelope (glycoproteins). They are produced abundantly in cells undergoing productive viral infection.

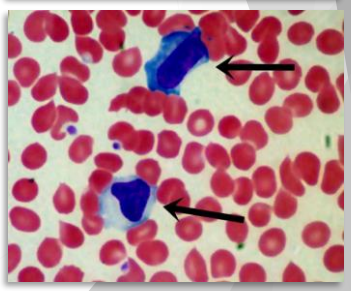
Pathogenesis and Pathology of EBV Infection

- EBV is commonly transmitted by infected saliva and initiates infection in the oropharynx. Viral replication occurs in epithelial cells (or surface B lymphocytes) of the pharynx and salivary glands. Infected B cells spread the infection from the oropharynx throughout the body. Most virus-infected cells are eliminated, but small numbers of latently infected lymphocytes persist for the lifetime of the host (one in 10^5–10^6 B cells).
- Primary infections in children are usually subclinical, but if they occur in young adults, acute infectious mononucleosis often develops. Mononucleosis is a polyclonal stimulation of lymphocytes. EBV-infected B cells synthesize immunoglobulin. Autoantibodies are typical of the disease, with heterophil antibody that reacts with antigens on sheep erythrocytes the classic autoantibody.
- Reactivations of EBV latent infections can occur. These are usually clinically silent.

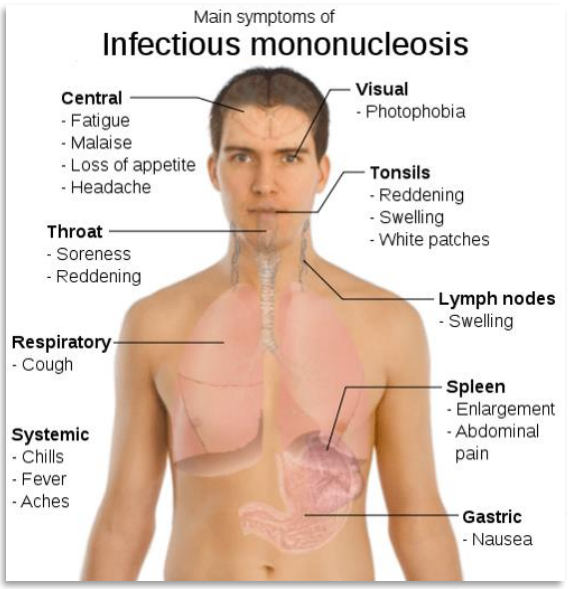
Clinical Findings of EBV Infection

- **Infectious Mononucleosis:** After an incubation period of 30–50 days, symptoms of headache, fever, malaise, fatigue, and sore throat occur. Enlarged lymph nodes and spleen are characteristic. Some patients develop signs of hepatitis.

- The typical illness is self-limited and lasts for 2–4 weeks. During the disease, there is an increase in the number of circulating white blood cells, with a predominance of lymphocytes. Many of these are large, **atypical T lymphocytes**. Low-grade fever and malaise may persist for weeks to months after acute illness. Complications are rare in normal hosts.

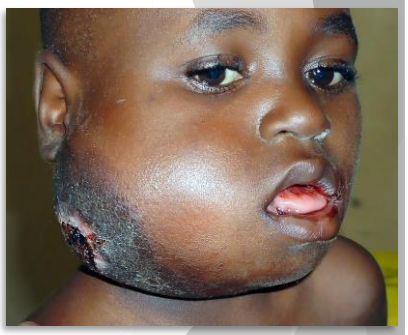


Infectious Mononucleosis (IM)



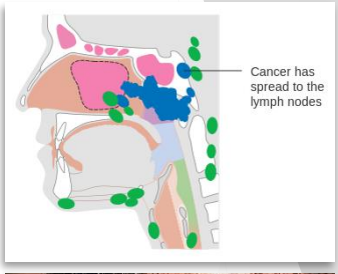
Clinical Findings of EBV Infection

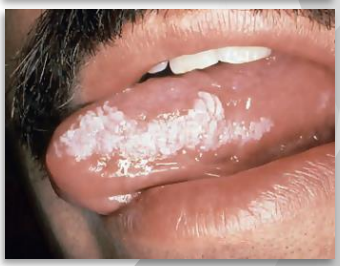
- **Cancer:** EBV is associated with Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin and NHLs, and gastric carcinoma.
- Burkitt lymphoma is **a tumor of the jaw in African children and young adults**. Most African tumors contain EBV DNA and express EBNA1 antigen.
- It is speculated that EBV may be involved at an early stage in Burkitt lymphoma by immortalizing B cells, with characteristic chromosome translocations that involve Ig genes and result in deregulation of expression of the *c-myc* proto-oncogene.



Clinical Findings of EBV Infection

- **Nasopharyngeal carcinoma** is a cancer of epithelial cells and is common in males of Chinese origin. EBV DNA is regularly found in nasopharyngeal carcinoma cells, and patients have high levels of antibody to EBV.
- AIDS patients are susceptible to EBV-associated **lymphomas** and **oral hairy leukoplakia**, a wart-like growth that develops on the tongue. Virtually all **CNS NHLs** are associated with EBV. In addition, EBV is associated with **classic Hodgkin disease**, with the viral genome detected in the malignant **Reed-Sternberg cells in up to 50% of cases**.





Laboratory Diagnosis of EBV Infection

Molecular Assays for Identification of Virus

- NAH is the most sensitive means of detecting EBV in patient materials.
- EBER RNAs are abundantly expressed in both latently infected and lytically infected cells and provide a useful diagnostic target for detection of EBV-infected cells by hybridization.
- Viral antigens can be demonstrated directly in lymphoid tissues and in nasopharyngeal carcinomas. During the acute phase of infection, about 1% of circulating lymphocytes will contain EBV markers; after recovery from infection, about one in 1 million B lymphocytes will carry the virus.

Laboratory Diagnosis of EBV Infection

Isolation of Virus

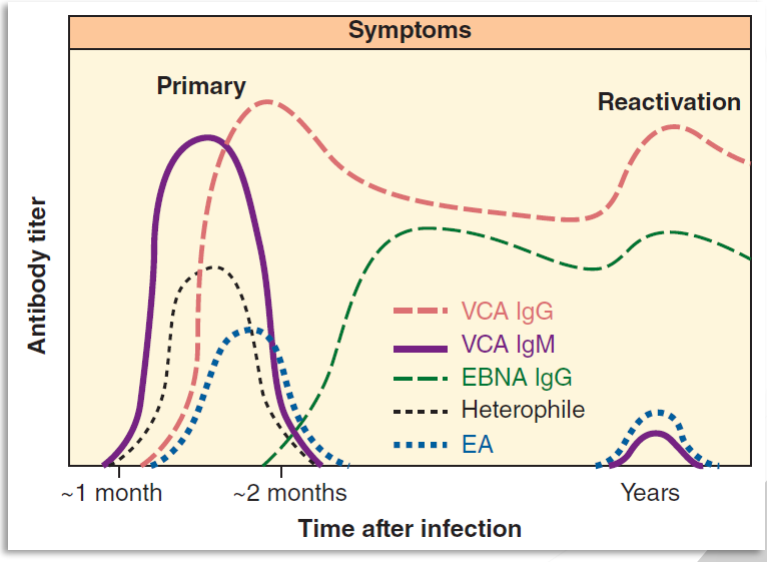
- EBV can be isolated from saliva, peripheral blood, or lymphoid tissue by immortalization of normal human lymphocytes, usually obtained from umbilical cord blood. This assay is laborious and time consuming (6–8 weeks), requires specialized facilities, and is seldom performed.
- EBV is present in the saliva of many immunosuppressed patients. Up to 20% of healthy adults will also yield virus-positive throat washings.

Laboratory Diagnosis of EBV Infection

Serology

- Common serologic procedures for detection of EBV antibodies include ELISA and IIFA tests using EBV-positive lymphoid cells.
- Early in acute disease, a transient rise in IgM antibodies to VCA occurs, replaced within weeks by IgG antibodies to this antigen, which persist for life.
- Slightly later, antibodies to the EA develop that persist for several months. Several weeks after acute infection, antibodies to EBNA and the membrane antigen arise and persist throughout life.

Typical pattern of antibody formation to EBV-specific antigens after a primary infection



Laboratory Diagnosis of EBV Infection

- The **less-specific** **heterophile agglutination test** may be used to diagnose EBV infections. In the course of IM, most patients develop transient heterophile antibodies that agglutinate sheep cells. Commercially available spot tests are convenient.
- Serologic tests for EBV antibodies require some interpretation. The presence of IgM to VCA is indicative of current infection. IgG to VCA is a marker of past infection and indicates immunity. EA antibodies are evidence of current viral infection.
- Antibodies to the EBNA antigens reveal past infection with EBV, although detection of a rise in anti-EBNA antibody suggests a primary infection. Not all persons develop antibody to EBNA.

Prevention, Treatment, and Control of EBV Infection

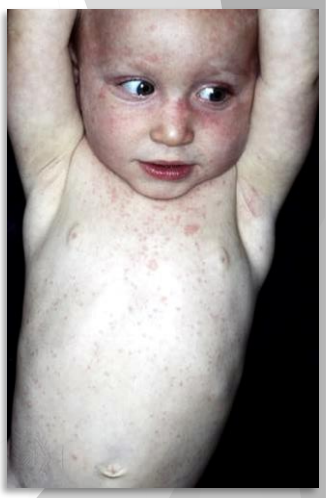
- There is no EBV vaccine available.
- Acyclovir reduces EBV shedding from the oropharynx during the period of drug administration, but it does not affect the number of EBV-immortalized B cells.
- Acyclovir has no effect on the symptoms of mononucleosis and is of no proved benefit in the treatment of EBV-associated lymphomas in immunocompromised patients.
- Adoptive transfer of EBV-reactive T cells shows promise as a treatment for EBV-related lymphoproliferative disease.

Human herpesvirus 6 (HHV-6)

- The **T-lymphotropic** HHV-6 was first recognized in 1986.
- The genetic arrangement of the HHV-6 genome resembles that of CMV.
- HHV-6 appears to be unrelated antigenically to the other known human herpesviruses except for some limited cross-reactivity with HHV-7. Isolates of HHV-6 segregate into two closely related but distinct antigenic groups (designated A and **B**).
- The virus grows well in CD4 T lymphocytes. Other cell types also support viral replication, including B cells and cells of glial and megakaryocyte origin.

Human herpesvirus 6 (HHV-6)

- Cells in the oropharynx must become infected because virus is present in saliva. It is not known which cells in the body become latently infected. **Human CD46 is the cellular receptor for the virus**.
- HHV-6 is widespread. It is estimated that more than 90% of children older than age 1 year and adults are sero-positive.
- Infections with HHV-6 typically occur in early childhood. This primary infection causes **exanthem subitum (roseola infantum, or "sixth disease")**, the mild common childhood disease characterized by a high fever and skin rash. **The 6B variant appears to be the cause of this disease**. The virus is associated with **febrile seizures in children**.



Human herpesvirus 6 (HHV-6)

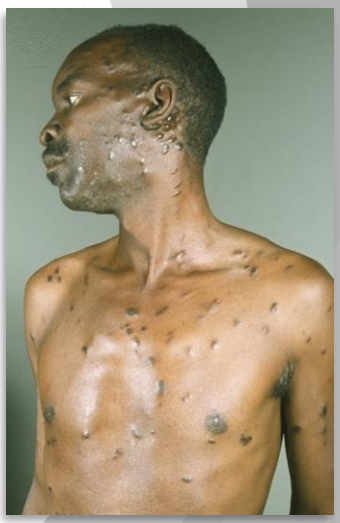
- The mode of transmission of HHV-6 is presumed to be **via oral secretions**.
- Infections persist for life. Reactivation appears to be common in transplant patients and during pregnancy. The consequences of reactivated infection remain to be determined.
- HHV-6 reactivation occurs in close to half of patients who undergo hematopoietic stem cell transplantation. Those reactivations occur soon after transplant and have been associated with delayed engraftment, central nervous system dysfunction, and increased mortality.

Human herpesvirus 7 (HHV-7)

- A T-lymphotropic human herpesvirus, designated HHV-7, was first isolated in 1990 from activated T cells recovered from peripheral blood lymphocytes of a healthy individual.
- HHV-7 is immunologically distinct from HHV-6, although they share about 50% homology at the DNA level.
- HHV-7 appears to be a ubiquitous agent, with most infections occurring in childhood but **later than the very early age of infection noted with HHV-6**. Persistent infections are established in salivary glands, and the virus can be isolated from saliva of most individuals.
- Similar to HHV-6, primary infection with HHV-7 has been linked with **roseola infantum in infants and young children**.

Human Herpesvirus 8 (KSHV)

- KSHV was first detected in 1994 in Kaposi sarcoma specimens.
- It is **lymphotropic** and is more closely related to EBV.
- Its genome (~165 kbp) contains numerous genes related to cellular regulatory genes involved in cell proliferation, apoptosis, and host responses.
- KSHV is the cause of Kaposi sarcomas, vascular tumors of mixed cellular composition, and is involved in the pathogenesis of body cavity-based lymphomas (**primary effusion lymphoma**) occurring in AIDS patients and of **multicentric Castleman disease**.

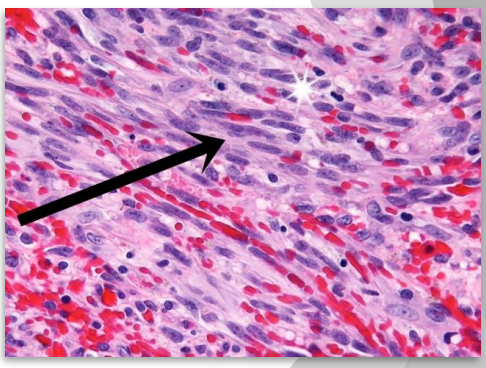


Human Herpesvirus 8 (KSHV)

- KSHV is not common as other herpesviruses (about 5% of the general population in US and northern Europe have serologic evidence of KSHV infection).
- **Contact with oral secretions** is the most common route of transmission. The virus can also be transmitted **sexually**, **vertically**, by blood, and through organ transplants. Viral DNA has also been detected in breast milk samples in Africa.
- Infections are common in Africa and are acquired early in life.
- Viral DNA can be detected in patient specimens using PCR. Disease is also diagnosed using histopathologic examination.
- Direct virus culture is difficult and impractical.

Human Herpesvirus 8 (KSHV)

- Serologic assays are available to measure persistent antibody to KSHV using indirect immunofluorescence, Western blot, and ELISA formats.
- Foscarnet, famciclovir, ganciclovir, and cidofovir have activity against KSHV.
- Level of KSHV replication is markedly reduced in HIV-positive patients on effective antiretroviral therapy, probably reflecting reconstituted immune surveillance against KSHV-infected cells.



Herpes B virus

- Infection occurs naturally in Old World monkeys (indigenous in macaques, mostly asymptomatic or causing vesicular oral and genital lesions).
- **It is highly pathogenic for humans**.
- Transmissibility is limited (via monkey bite, scratched exposure of broken skin to tissue fluid).
- Infections that do occur are associated with **a high mortality rate** (~60%).
- B virus disease of humans is an **acute ascending myelitis** and **encephalomyelitis**.

Herpes B virus

- It is designated **cercopithecine herpesvirus 1**, replacing the older name of *Herpes simiae*. Its genome organization is similar to that of HSV.
- Animal workers and persons handling macaque monkeys, including medical researchers, veterinarians, pet owners, and zoo workers, are at risk.
- There is no specific treatment after the clinical disease is manifest.
- Treatment with acyclovir is recommended immediately after exposure.
- No vaccine is available.
- The risk of B virus infections can be reduced by proper procedures in the laboratory and in the handling and management of macaque monkeys. This risk makes macaques unsuitable as pets.