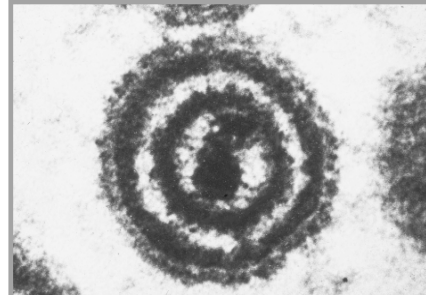


Common Features of Herpesviruses

- Morphology
- Basic mode of replication
- Primary infection followed by latency
- Ubiquitous
- Ability to cause **recurrent** infections (reactivation of latent virus), **reinfections** (with a new virus), **persistent** infections (chronic low grade virus multiplication) **immortalizing infections** (EBV only)

Human Herpesvirus (VZV)

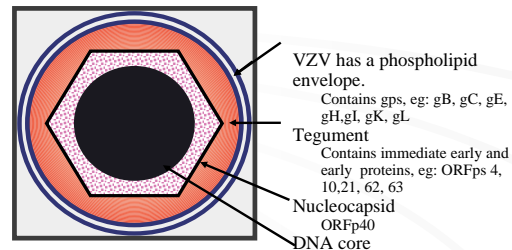
phospholipid envelope, tegument, icosahedral capsid, DNA core



8 Human Herpesviruses, 3 categories

- Alpha: short reproductive cycle, variable host range, latent in sensory neurons
 - Herpes simplex virus (HSV 1, 2)
 - Varicella-zoster virus (VZV)
- Beta: long reproductive cycle, narrow host range, latent in lymphoid cells & others (salivary glands, kidney)
 - Cytomegalovirus (CMV)
 - HHV6, HHV 7
- Gamma: narrow host range; latent in lymphoid cells, associated with tumors
 - Epstein Barr Virus (EBV)
 - Kaposi Sarcoma Virus (KSH, HHV8)

VZV is a typical herpesvirus

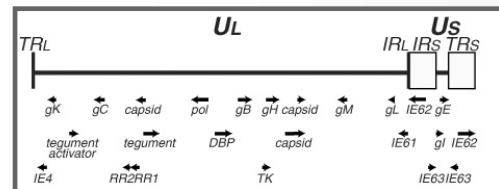


Human Herpesviruses

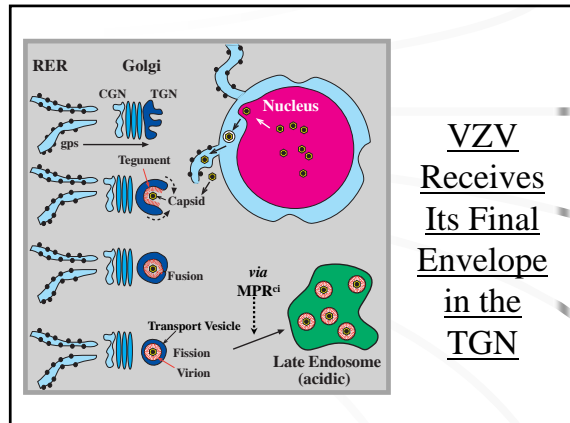
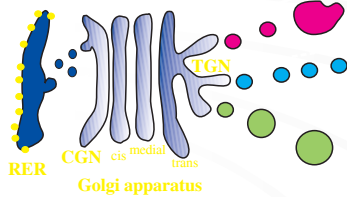
- Replication (lytic infection) occurs in a cascade
 - Latency occurs when the cascade is interrupted
- Transcription of viral genome and protein synthesis (cascade of gene expression), essential and luxury
 - 1. immediate early (IE): regulation of gene expression, DNA binding
 - 2. early (E): more transcription factors, enzymes, DNA polymerase
 - 3. late (L): structural proteins
- Encode targets for antiviral therapy
 - TK, DNA polymerase

Varicella-zoster virus

- The smallest of the herpesviruses
 - 125,000 base pairs
 - 70 Open reading frames (ORFs)
- Receptors: heparan sulfate, mannose-6 phosphate receptor

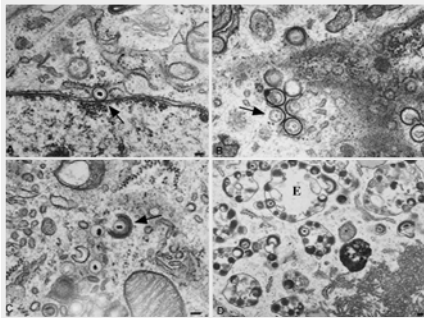


MPRs sort lysosomal enzymes and target them to endosomes



VZV
Receives
Its Final
Envelope
in the
TGN

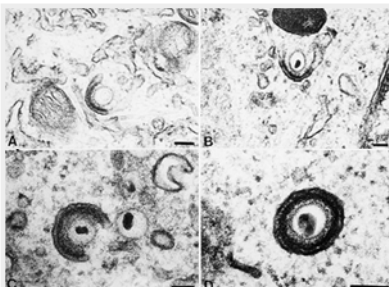
Steps in the assembly and intracellular transport of VZV



Herpes simplex virus (HSV)
Infection (alpha)

- Cellular receptors are heparan sulfate, HVEM, Nectin-1, 2
 - Members of the immunoglobulin protein and TNF families
- Glycoproteins B, D, H, L promote attachment to cells and viral fusion with cell membrane
 - Viral proteins are released promoting gene transcription, cytotoxicity
- Lytic infection results in cell death
 - Virions are released or spread from cell to cell
- Latent infection occurs in sensory neurons
 - Latency associated transcripts (LATS)
 - Minimal transcription of DNA, no translation

VZV receives its final envelope
in the TGN



- Cytosolic nucleocapsids and tegument are wrapped by TGN cisternae.
- Concave surface = viral envelope.
- Convex surface = transport vesicle.

HSV Infections

- Classification: primary, non-primary, first episode, recurrent, reinfection
- HSV-1: above belt, HSV-2: below belt
- Reactivation: trauma, sunlight, stress
 - Despite antibodies
 - May be related to deficient gamma IF response
 - May recur in same area of skin (unlike VZV)
- Many/most infections are asymptomatic
 - asymptomatic shedding can transmit HSV to others
- Host factors: immunocompromised, newborn baby

Herpes simplex virus (HSV)

Infections

- Mucocutaneous, neonatal, CNS
- Type 1: gingivostomatitis, whitlow, keratitis, encephalitis, eczema herpeticum
- Type 2: genital, meningitis, neonatal
Main serious clinical problems are in newborn, and immunocompromised hosts
- Healthy hosts may develop gingivostomatitis, encephalitis, acute and recurrent genital HSV
- Disease from viral- and immuno-pathology

HSV causes about 1000 cases of encephalitis annually in USA

- Most common form of focal encephalitis in USA
- Primary or recurrent HSV-1 ; skin lesions may be present (not helpful for diagnosis)
- Symptoms, signs: headache, fever, personality change, focal seizures, abnormal EEG, CT, MR
- Differential diagnosis: TB meningitis, arbovirus, enterovirus, flavivirus, mycoplasma, tumor, toxoplasmosis, aneurysm
- Diagnosis: CSF culture is usually negative, but PCR is often positive for HSV
- Treat (ACV) if suspect disease; prognosis better in children than adults; early therapy is best

Primary HSV-1 gingivostomatitis



Perinatal HSV is usually due to Type 2 virus

- 95% neonatal, 5% congenital
- Usually the mother is asymptomatic
- Attack rate >10 times higher in maternal primary infection than recurrence; attack rate about 50%
- Clues: skin vesicles in 70%, fever, seizures, pneumonia, DIC, conjunctivitis
- Diagnosis: immunofluorescence, culture, PCR
- Treat all infants with this diagnosis, even if all they have are a few skin vesicles but seem otherwise well

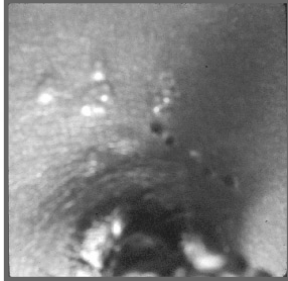
Herpetic whitlow, HSV 1



Neonatal HSV-1



Neonatal HSV-2



Natural History of VZV

- **Primary infection: varicella**
 - Highly contagious (airborne)
 - Complications: bacterial superinfection, encephalitis, pneumonia, congenital syndrome
- **Secondary infection: zoster**
- Zoster is due to reactivation of latent VZV
 - DNA, RNA, proteins in ganglia at autopsy
 - Zoster in a few vaccinees caused by Oka vaccine
 - From low cell-mediated immunity (CMI) to VZV
- No asymptomatic shedding of VZV as with HSV

Neonatal HSV Infection, 1600 cases annually

- Skin, eye, mucous membrane (40%)
 - Skin vesicles
 - Good prognosis with early treatment
 - Untreated 75% develop disseminated infection
- CNS Infection (35%)
 - Fever, lethargy, seizures, abnormal CSF
 - 50% mortality; major sequelae if survive
- Disseminated disease (25%)
 - Hepatosplenomegaly, jaundice, hepatitis, pneumonia
 - 2/3 develop skin vesicles
 - 70% mortality



Varicella is a generalized illness. Infectious virions are produced in the skin vesicles.

Neonatal HSV

- Diagnosis: immunofluorescence, culture, PCR
 - Antibody titers are not useful
- Treat all newborn infants with possible HSV
 - Begin therapy while awaiting diagnostic results
 - Specific treatment (ACV) is very well tolerated
- Recurrent skin vesicles are associated with a poorer prognosis
 - may re-treat with ACV
 - May give 6 weeks of oral ACV

Zoster is initially localized.



- Limited to 1-3 dermatomes.
- May disseminate in immunocompromised hosts.

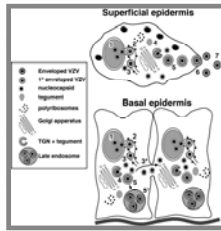
In the body VZV spreads from cell-to-cell

- In varicella, VZV is transported from the respiratory mucosa to the blood (viremia) in T cells, where virus is not accessible to antibodies.
 - Because cell-to-cell spread is slow, the incubation period of varicella is long (2 weeks).
 - Slow spread prevents host from being overwhelmed before the immune response develops
- T helper (TH1) and cytotoxic T cells are required for host control of virus

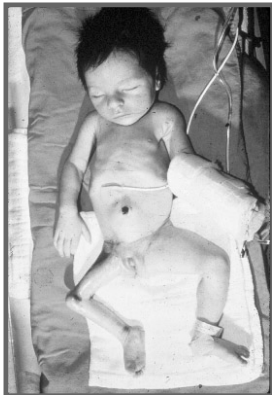


Fatal neonatal varicella

VZV spreads in two ways



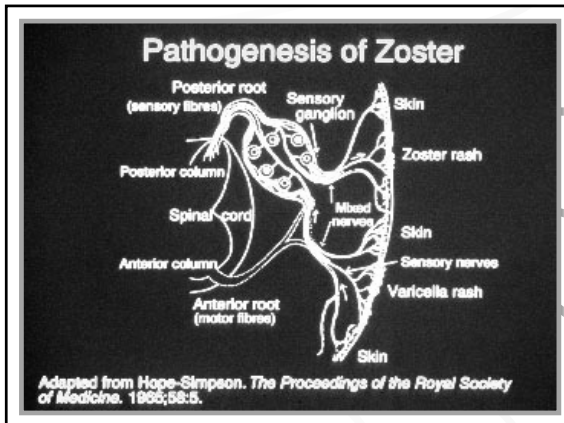
Zoster in a 3 month old



Congenital varicella syndrome

VZV In the Immunocompromised

- Varicella is likely to be severe
 - Prevent or modify with pre-formed antibodies just after exposure
 - Virus spreads from cell-cell in body
 - requires CMI (cellular immunity) for host defense
 - Treat most immunocompromised patients immediately with acyclovir
- The frequency of zoster is increased
 - Probably related to low CMI response
 - Likely to suffer post-herpetic neuralgia (PHN) (also elderly)



Varicella Vaccine

Major complaint afterwards: mild rash in 5%

- 1 month after vaccination; transmission to others is rare
- This vaccine is extremely safe

85% completely protected; 15% partial immunity

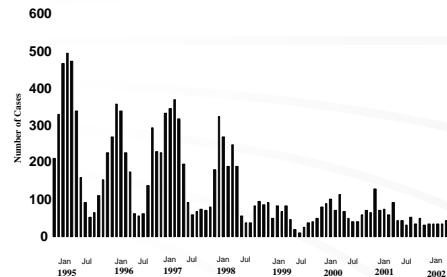
There is little evidence for waning immunity

Subsequent zoster is rare

Latent Infection with VZV

- Latent infection in dorsal root ganglia (DRG)
- 6 of 68 genes (also RNA and proteins) expressed during latency
- Proteins of regulatory genes are expressed in cell cytoplasm, not nucleus
- Suggests regulatory proteins are blocked from normal action, leading to inhibition of cascade of gene expression preventing lytic infection from occurring (latency)
- Latency is established when cell-free VZV in skin vesicles invades neurons

Varicella, Antelope Valley, CA



Varicella Vaccine

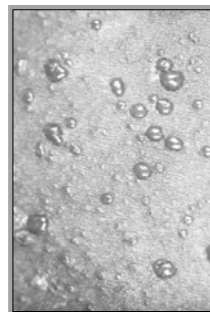
Only herpesvirus for which there is a vaccine

Live, attenuated, infectious virus (Oka strain)
Licensed for routine use in healthy susceptible individuals in US, in 1995

Recently there has been a marked decrease in varicella, in all age groups
– Indicates herd immunity

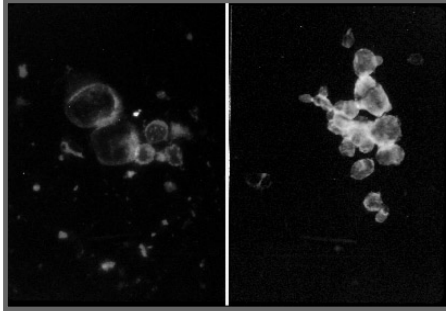
- Contraindications: pregnancy, immunocompromised, allergy to vaccine components

The rash of VZV is vesicular.



- Vesicular fluid is highly infectious.
– Well-formed virions are suspended in it.

Indirect immunofluorescence
To diagnose VZV, HSV



Cytomegalovirus (CMV)

- Largest of the herpesviruses (mRNA too)
 - 208 ORFs; gB, gH
 - immune evasion
 - Down regulation of MHC class I expression to reduce effectiveness of cytotoxic T cells
- Host defense: cellular not humoral immunity
- Latency in bone marrow precursors of monocytic peripheral blood cells
 - Differentiation of monocytes into macrophages due to antigenic stimulation reactivates CMV
 - Adverse effects on transplantation

Laboratory
Methods for Diagnosis

- Culture (difficult), DFA, PCR, cytology on skin rash (Tzanck)
 - Can distinguish the Oka virus from wild type virus (PCR)
- Antibody titers, IgG (ELISA)
 - Acute serum, early in illness
 - Convalescent serum, 10-14 days after onset
- Antibody titers, IgM
 - False positives and false negatives can be a problem

Cytomegalovirus (CMV)

- In healthy adult hosts infection is usually subclinical
 - Mononucleosis-like syndrome occurs but is rare
- Severe, opportunistic infections in immunocompromised hosts
 - AIDS patients, after transplantation
- Fetal (congenital) infections: can be severe
- Perinatal infections: of little consequence
 - At birth (maternal secretions), from breast milk

Acyclovir (ACV) is useful to
treat HSV, VZV

- Antiviral activity only in infected cells (TK)
- Sensitivity: HSV1, >HSV2, >VZV (EBV, CMV)
- Toxicity is unusual: gastrointestinal, neurologic (headache, seizures, delirium); anemia, thrombocytopenia, bone marrow suppression
- Resistance is a concern, especially in HIV-infected patients
- Newer drugs: famciclovir, valacyclovir
 - Administered orally and less frequently than ACV because better gastrointestinal absorption

Congenital CMV Infection

- Most common congenital viral infection in US
 - 40,000 annual cases (1% of all infants)
 - 3,000 symptomatic at birth (jaundice, petechiae, microcephaly, prematurity)
 - 8,000 with sequelae (deafness, retardation)
- Risk to the infant is highest in first trimester (13 weeks) maternal infection
 - primary maternal infection poses greatest risk
 - the fetus is not always protected when an “immune” mother is re-infected with a different strain of CMV
- Distinguish between congenital and perinatal
 - In congenital infection urine is culture +for CMV in first 3 weeks of life

CMV Infections in the Immunocompromised (including AIDS)

- Frequent
- May be primary or recurrent (reactivation from latency)
- Can have reinfection with a new strain
- Symptoms/signs: fever, pneumonia, retinitis, colitis, lymphadenopathy, rash, encephalitis, neutropenia, etc.
- Diagnosis is difficult; must distinguish between true infection/disease and persistent virus
 - Asymptomatic infections occur

Transmission of CMV

- Close personal contact
 - Sexual, day care (saliva, tears, urine)
 - Virus is not usually airborne
 - Cell-associated virus, no skin lesions
 - Spread from secretions, on hands
- Intrauterine/birth/breast milk
- Transfusion
- Transplantation

Diagnosis of CMV

- Histology: has limitations (not specific)
 - Basophilic inclusion bodies
 - H&E, Pap staining
- Cell culture
 - Cytopathic effect, immunofluorescence
- Serology: acute and convalescent antibody titers are of limited value
 - False positive and false negative IgM titers
- In situ hybridization
- PCR

Control of CMV

- Hand washing (eg, after diapering)
- Condoms, abstinence
- Beware of blood
 - Use seronegative, irradiated, filtered blood for high risk patients
- Testing for CMV in transplantation (donor, recipient)
- Vaccine still not available

Treatment of CMV

- Ganciclovir
 - Phosphorylation by viral enzymes causes inhibition of viral DNA polymerase (related to acyclovir); toxicity: bone marrow suppression
 - Foscarnet
 - Inhibits viral DNA polymerase; renal, metabolic toxicity
 - Cidofovir
 - Inhibits viral DNA polymerase
 - Very toxic (renal, uric acid increase)
- Pre-emptive approach
Identify infection before the illness
- Treatment used mostly for immunocompromised patients

Epstein-Barr Infections (gamma)

- Major glycoprotein is gp 350 which binds to CD21 on B cells (C3d complement receptor)
 - Patients with x-linked agammaglobulinemia can't be infected
- Seropositive persons shed virus in saliva (lytic)
- Virus utilizes immune evasion
 - Genes that mimic interleukin (IL) 10 and decrease interferon (IF) response, inhibit apoptosis
- Experimental therapy for immunocompromised patients with severe infections/tumors (lymphoproliferative disease)
 - Decrease immunosuppressive therapy if possible
 - Monoclonal antibodies (rituximab)
 - Infusion of leukocytes

Epstein-Barr Infections (EBV)

- Infectious mononucleosis, nasopharyngeal carcinoma, lymphomas (including Burkitt's), oral hairy leukoplakia (lytic infection), X-linked proliferative disease (males only)
- B cells are latently infected in mononucleosis; T cells (atypical lymphocytes) are the host response
- Latency develops in memory B cells
- EBV is not related to chronic fatigue syndrome, but rarely severe chronic illness follows mononucleosis
- In mononucleosis, give steroids if airway obstruction, hemolytic anemia, severe cardiac, neurologic disease (no specific antiviral therapy)

Herpesvirus 8 (KHSV)

- Closely related to EBV
- Encodes for human proteins (piracy)
 - IL-6, Bcl-2 (anti-apoptosis), chemokines
- Infections are rare in children
 - Can cause non-specific fever and rash illness
- Causes Kaposi's Sarcoma
 - Elderly
 - HIV-infected
- Causes primary-effusion lymphoma
- Castleman's disease (lymphoma-like)

Diagnosis of Mononucleosis

- Usually occurs in young adults
- Symptoms, signs: fever, adenopathy, exudative pharyngitis, rash (ampicillin) hepatosplenomegaly fatigue
- Positive heterophile antibody (monospot)
- EBV specific antibodies
 - Anti VCA (develops **early**, persists)
 - Anti EBNA (develops **late**, persists)
 - Positive ab by VCA, neg ab by EBNA = acute mononucleosis

Summary: Herpesvirus Infections

- Particularly affect newborns, elderly, immunocompromised
 - Congenital (**CMV**, **VZV**) vs neonatal (**HSV**, **VZV**); primary maternal infections high risk
- Primary, latent, recurrent, reinfections
- Best diagnostic tool: PCR
- Antiviral therapy: HSV, VZV, CMV
- EBV and HHV8 cause tumors
- Vaccine now available against to prevent chickenpox (varicella)

Herpesviruses 6, 7

- Herpesvirus 6 (beta, like CMV)
 - Roseola in infants (rash, fever, seizures)
 - outcome of latency in CNS not understood
 - Fevers in immunosuppressed
 - Rare mononucleosis syndrome in adults
- Herpesvirus 7 (beta, like CMV)
 - Fevers in immunocompromised (HIV)
- Diagnosis, treatment are not fully developed
 - Most infections are self-limited