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)

8 Human Herpesviruses, 3 categories

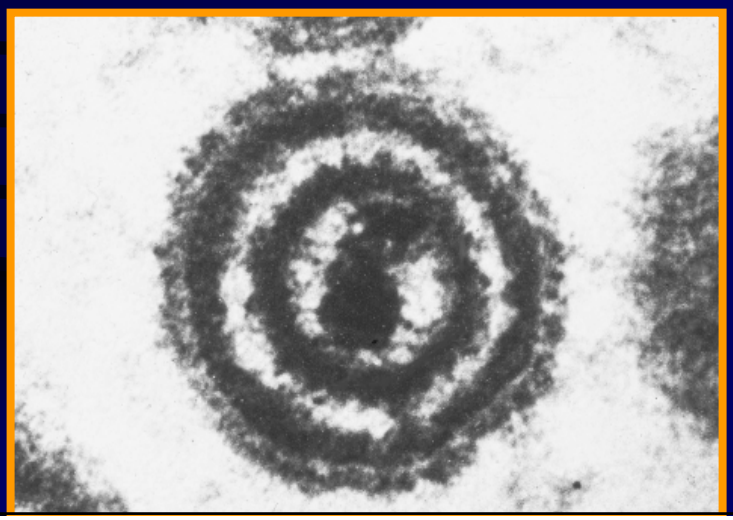
- Alpha: short reproductive cycle,variable host range, latent in sensory neurons
  - Herpes simplex virus (HSV 1, 2)
  - Varicella-zoster virus (VZV)
- Beta: long reproductive cycle, narrow host range, latent in lymphoid cells & others (salivary glands, kidney)
  - Cytomegalovirus (CMV)
  - HHV6, HHV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

Human Herpesviruses

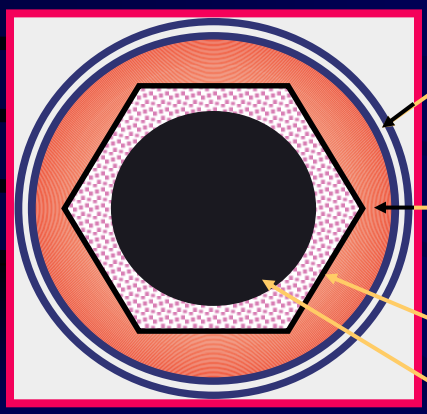
- Replication (lytic infection) occurs in a cascade
  - Latency occurs when the cascade is interrupted
- Transcription of viral genome and protein synthesis (cascade of gene expression), essential and luxury
  - 1. immediate early (IE): regulation of gene expression, DNA binding
  - 2. early (E): more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

Human Herpesvirus (VZV)

phospholipid envelope, tegument, icosahedral capsid, DNA core



VZV is a typical herpesvirus



VZV has a phospholipid envelope.
- Contains gps, eg: gB, gC, gE, gH,gI, gK, gL

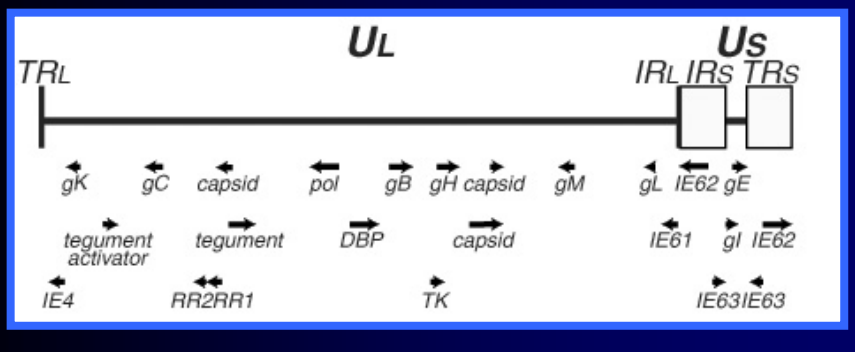
Tegument
- Contains immediate early and early proteins, eg: ORFps 4, 10,21, 62, 63

Nucleocapsid
- ORFp40

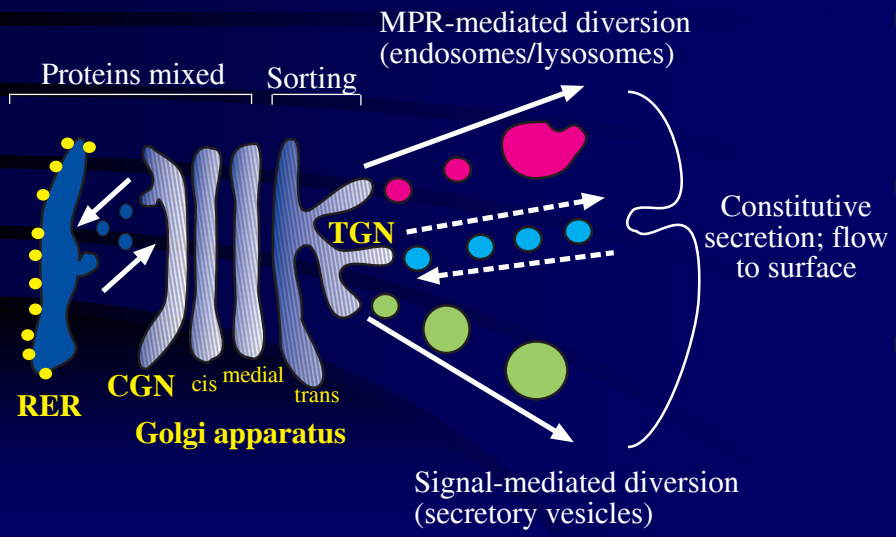
DNA core

Varicella-zoster virus

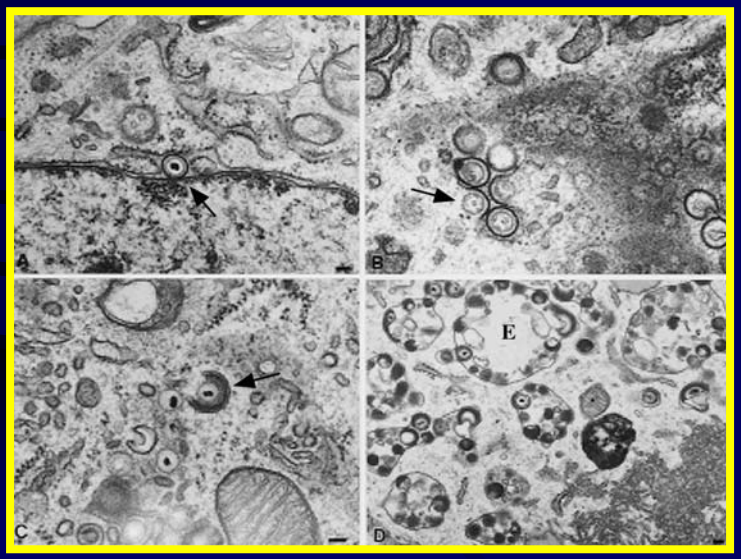
- The smallest of the herpesviruses
  - 125,000 base pairs
  - 70 Open reading frames (ORFs)
- Receptors: heparan sulfate, mannose-6 phosphate receptor



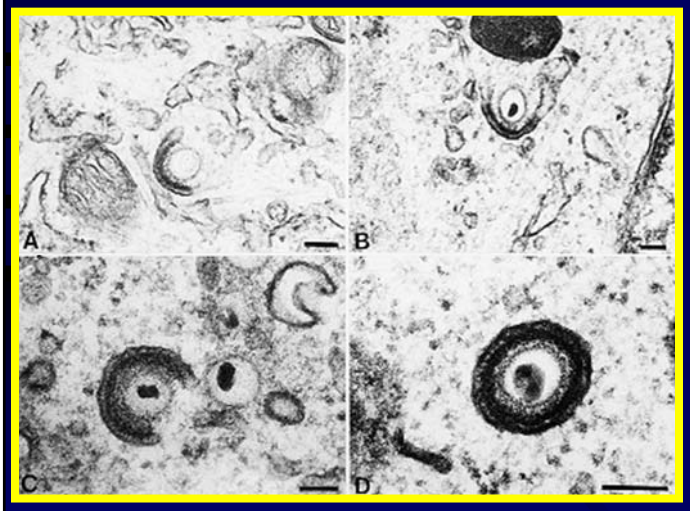
MPRs sort lysosomal enzymes and target them to endosomes



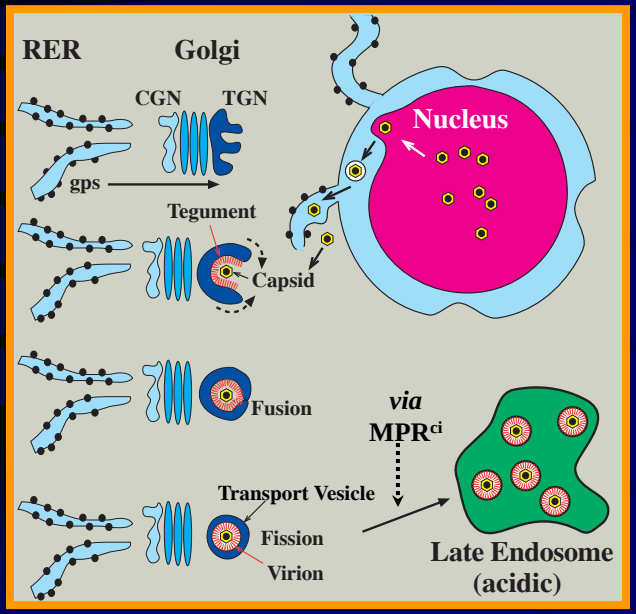
Steps in the assembly and intracellular transport of VZV



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.



VZV Receives Its Final Envelope in the TGN

Herpes simplex virus (HSV) Infection (alpha)

- Cellular receptors are heparan sulfate, HVEM, Nectin-1, 2
  - Members of the immunoglobulin protein and TNFfamilies
- 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

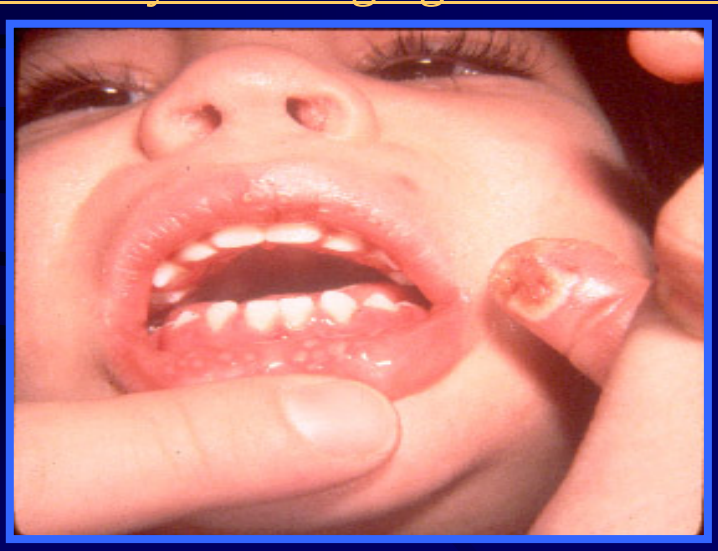
HSV Infections

- 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

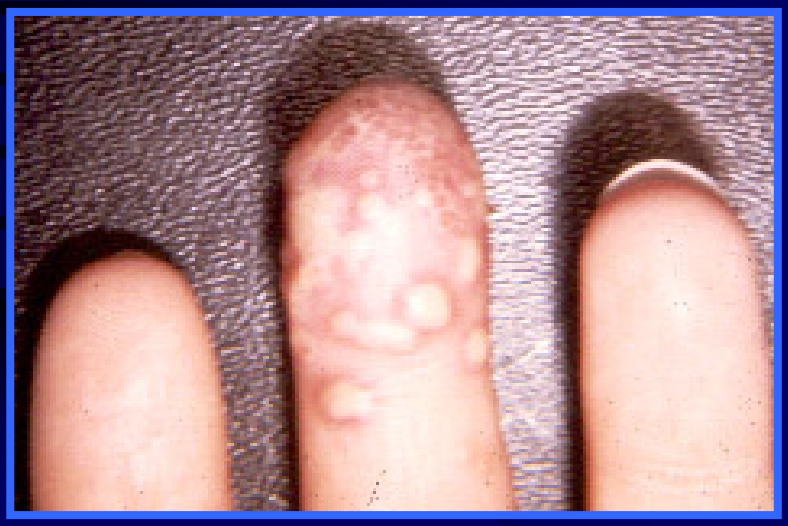
Herpes simplex virus (HSV) Infections

- 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

Primary HSV-1 gingivostomatitis



Herpetic whitlow, HSV 1



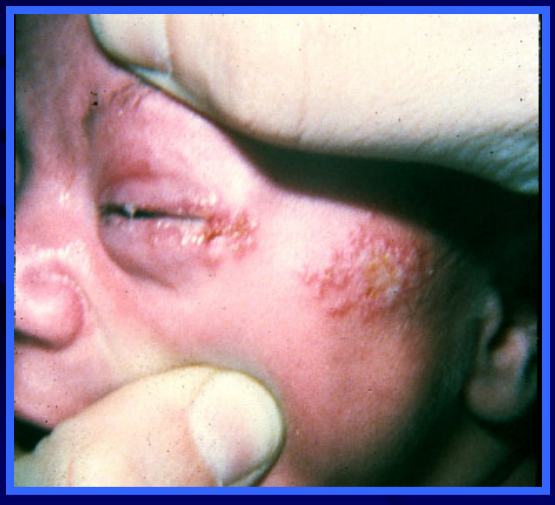
HSV causes about 1000 cases of encephalitis annually in USA

- 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

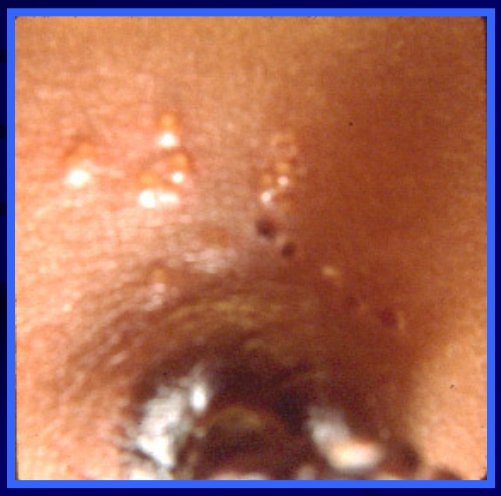
Perinatal HSV is usually due to Type 2 virus

- 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

Neonatal HSV-1



Neonatal HSV-2



Neonatal HSV Infection, 1600 cases annually

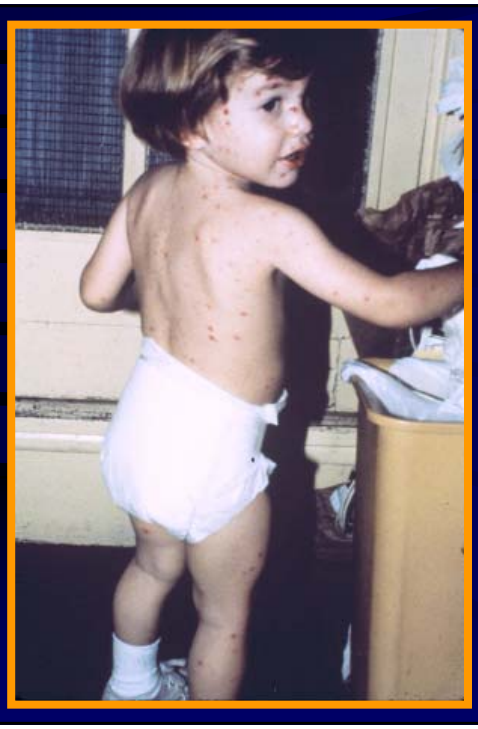
- Skin, eye, mucous membrane (40%)
  - Skin vesicles
  - Good prognosis with early treatment
  - Untreated 75% develop disseminated infection
- CNS Infection (35%)
  - Fever, lethargy, seizures, abnormal CSF
  - 50% mortality; major sequelae if survive
- Disseminated disease (25%)
  - Hepatosplenomegaly,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

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 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

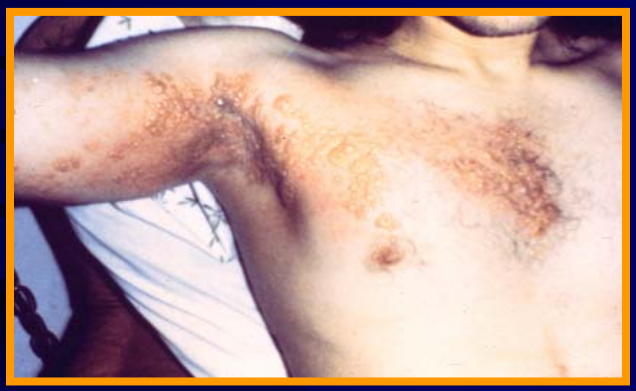
Natural History of VZV

- **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**



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

Zoster is initially localized.

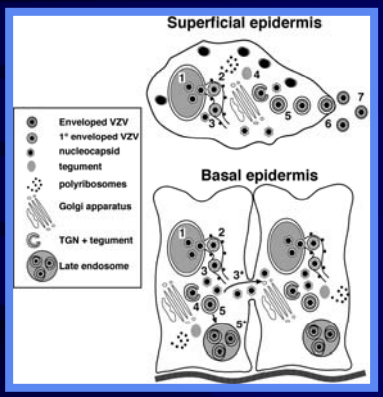


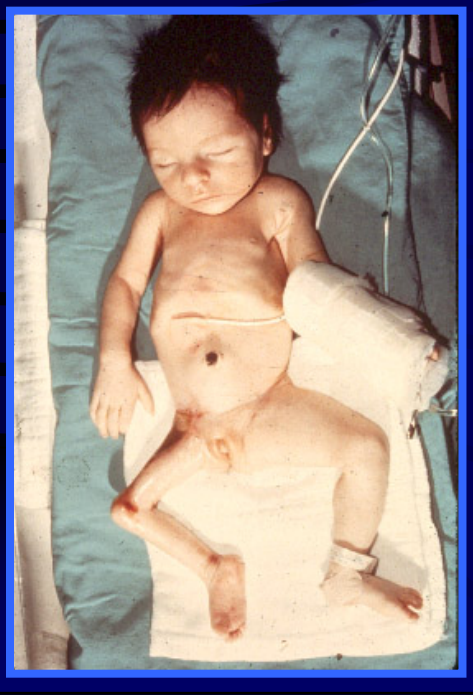
- Limited to 1-3 dermatomes.
- May disseminate in immunocompromised hosts.

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

VZV spreads in two ways

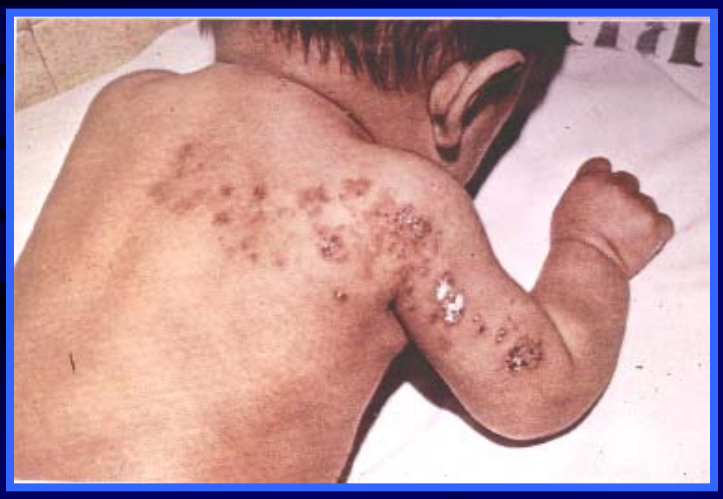




Congenital varicella syndrome

Fatal neonatal varicella

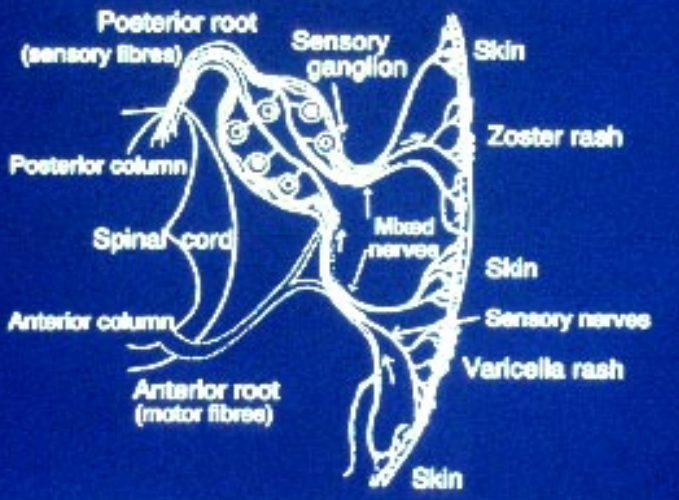
Zoster in a 3 month old



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)

Pathogenesis of Zoster



Adapted from Hope-Simpson. *The Proceedings of the Royal Society of Medicine*. 1965;58:5.

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 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

Varicella Vaccine

Major complaint afterwards: mild rash in 5%

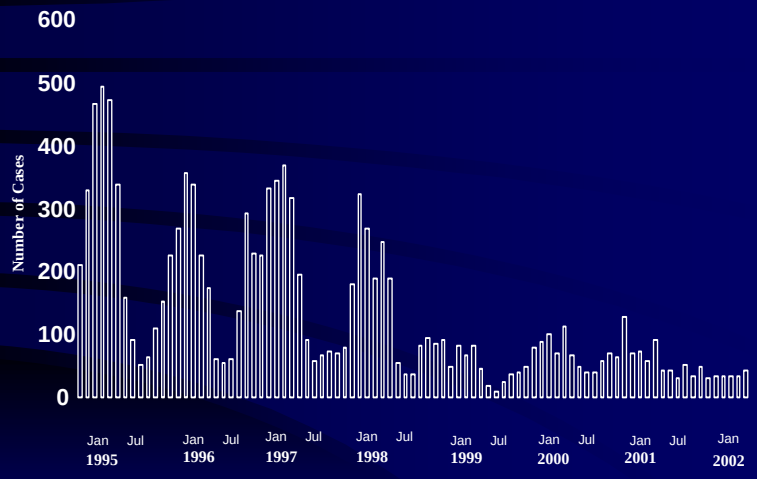
- 1 month after vaccination; transmission to others is rare
- This vaccine is extremely safe

85% completely protected; 15% partial immunity

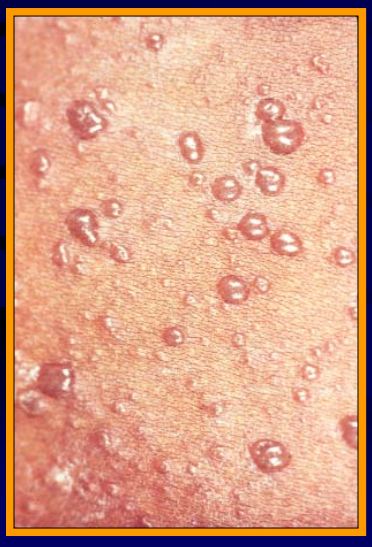
There is little evidence for waning immunity

Subsequent zoster is rare

Varicella, Antelope Valley, CA

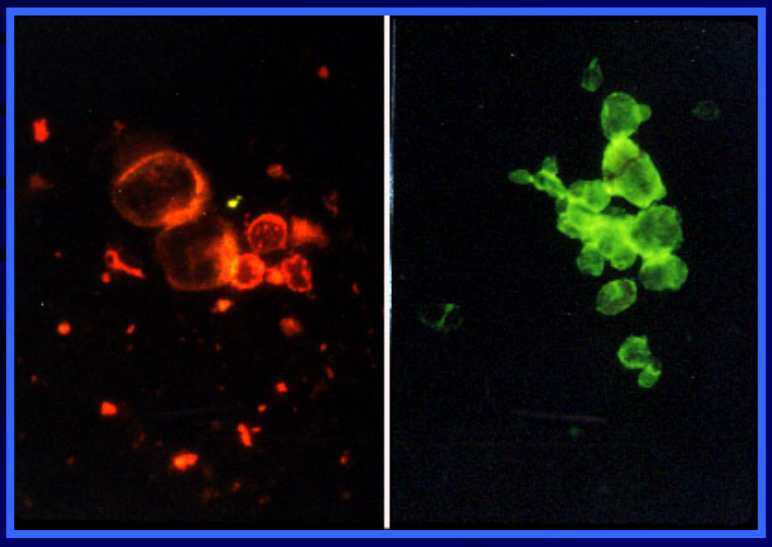


The rash of VZV is vesicular.



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

Indirect immunofluorescence To diagnose VZV, HSV



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

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, delerium); anemia, thrombocytopenia, bone marrow suppression
- Resistance is a concern, especially in HIV-infected patients
- Newer drugs: famciclovir, valacyclovir
  - Administered orally and less frequenly than ACV because better gastrointestinal absorption

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

Cytomegalovirus (CMV)

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

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

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

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

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

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

Epstein-Barr Infections (gamma)

- Major glycoprotein is gp 350 which binds to CD21 on B cells (C3d complement receptor)
  - Patients with x-linked agammaglobuinemia 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)

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 aby VCA, neg aby EBNA = acute mononucleosis

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

Herpesvirus 8 (KHSV)

- Closely related to EBV
- Encodes for human proteins (piracy)
  - IL-6, Bcl-2 (anti-apotosis), cheomkines

  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)

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)