VZV, EBV, and HHV-6-8

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Human Herpesviruses

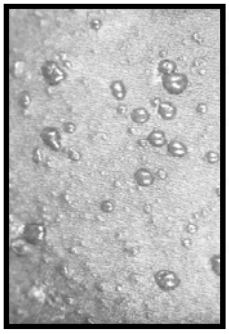
- Replication (lytic infection) occurs in a cascade
  - Latency occurs when the cascade is interrupted
- Transcription of viral genome and protein synthesis (cascade of gene expression), essential and luxury
  - 1. immediate early (IE): regulation of gene expression, DNA binding
  - 2. early (E): more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

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)

The rash of VZV is vesicular.



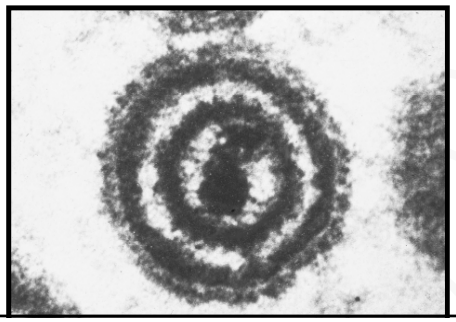
- Vesicular fluid is highly infectious.
  - Well-formed virions are suspended in it.

8 Human Herpesviruses, 3 categories

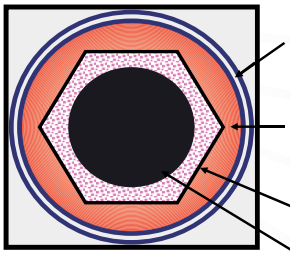
- Alpha: short reproductive cycle,variable host range, latent in sensory neurons
  - Herpes simplex virus (HSV 1, 2)
  - Varicella-zoster virus (VZV)
- Beta: long reproductive cycle, narrow host range, latent in lymphoid cells & others (salivary glands, kidney)
  - Cytomegalovirus (CMV)
  - HHV6, HHV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

Human Herpesvirus (VZV)

phospholipid envelope, tegument, icosahedral capsid, DNA core



VZV is a typical herpesvirus



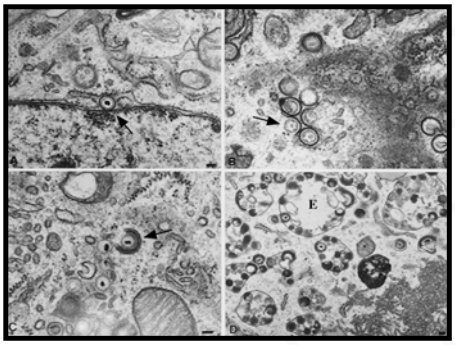
VZV has a phospholipid envelope.
- Contains gps, eg: gB, gC, gE, gH,gI, gK, gL

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

Nucleocapsid
- ORFp40

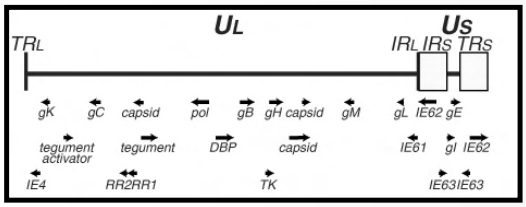
DNA core

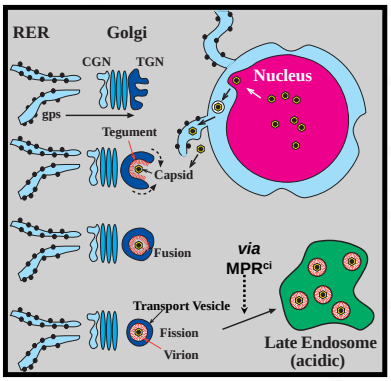
Steps in the assembly and intracellular transport of VZV



Varicella-zoster virus

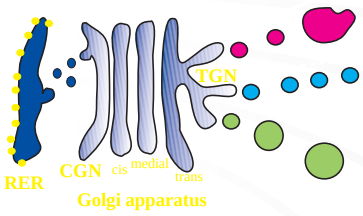
- The smallest of the herpesviruses
  - 125,000 base pairs
  - 70 Open reading frames (ORFs)
- Receptors: heparan sulfate, mannose-6 phosphate receptor (MPR), insulin degrading enzyme (IDE)



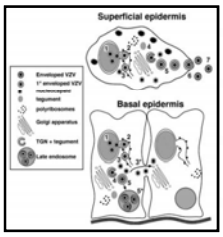


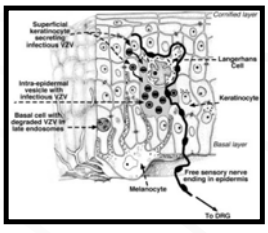
VZV Receives Its Final Envelope in the TGN

MPRs sort lysosomal enzymes and target them to endosomes

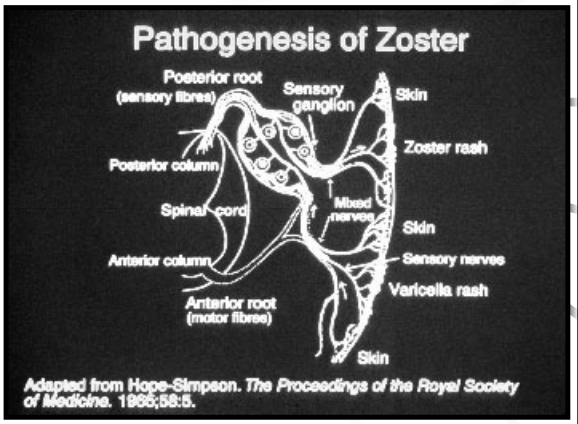


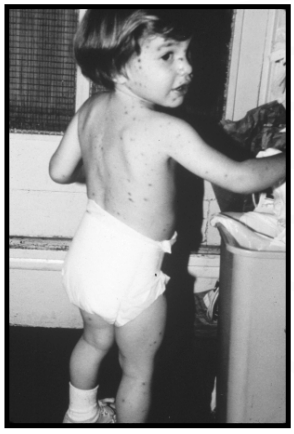
Hypothesis: VZV latency is established by free virions that infect sensory nerve endings





VZV spreads in two ways



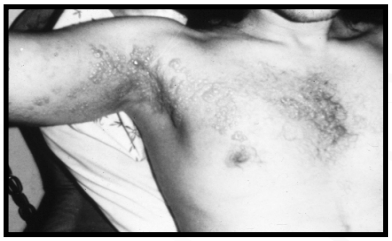


Varicella is a generalized illness. Infectious virions are produced in the skin vesicles.

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

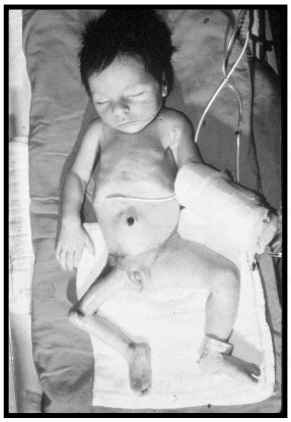
Zoster is initially localized.



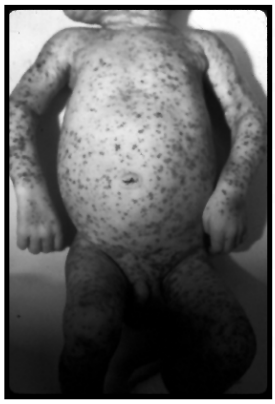
- Limited to 1-3 dermatomes.
- May disseminate in immunocompromised hosts.

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**



Congenital varicella syndrome

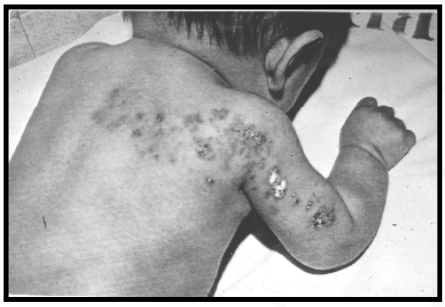


Fatal neonatal varicella

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

Zoster in a 3 month old



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

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

Live attenuated; stimulates primary immunity

Major complaint afterwards: mild rash in 5%

- 1 month after vaccination; transmission is rare
- Vaccine is extremely safe

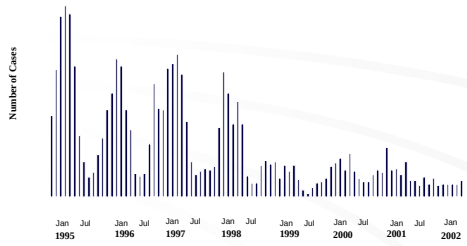
85% completely protected; 15% partial immunity

There is little evidence for waning immunity

Subsequent zoster is rare

Same vaccine (much higher dose) also used successfully to prevent zoster in the elderly (different mechanism of action… stimulates CMI to VZV)

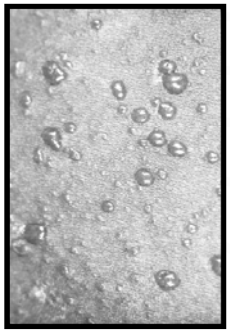
Varicella, Antelope Valley, CA



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

The rash of VZV is vesicular.

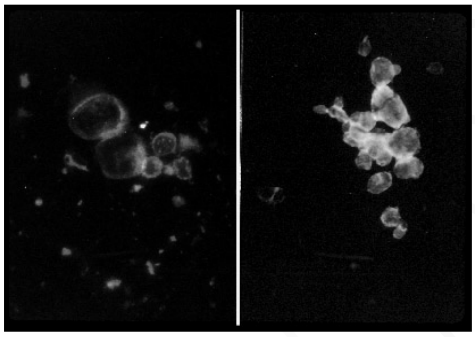


- Vesicular fluid is highly infectious.
  - Well-formed virions are suspended in it.

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 frequently than ACV because better gastrointestinal absorption

Indirect immunofluorescence To diagnose VZV, HSV



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

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) and zoster (shingles)

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), 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)