Herpesviruses

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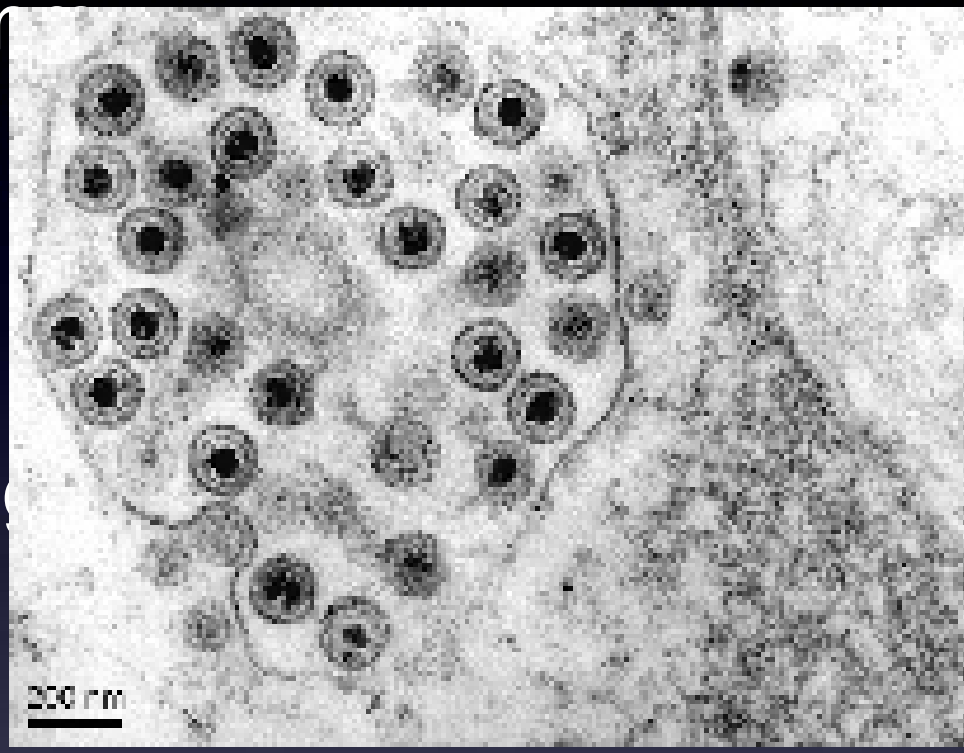
Structure and Composition

- Spherical iscoahedron, 150-200 n
- Double-stranded DNA, linear
- More than 35 proteins
- Enveloped
- Replication from nucleus (buddin
- Features
  - Encode many enzymes
  - Establish latent infections
  - Lifelong persistence
  - Significant cause of death in immunocompromised hosts
  - Some can cause cancers



lassification (human viruses)

ubfamilies

- Alpha
- Beta
- Gamma

pecies

- Simplex 1 (HHV-1) (alpha)
- Simplex 2 (HHV-2) (alpha)
- Varicella (HHV-3) (alpha)
- Epstein-Barr (HHV-4) (gamma)
- Cytomegalovirus (HHV-5) (beta)
- HHV-6 (beta)
- HHV-7 (beta)

eplication of HSV

rus attachment and membrane fusion

- Viral host shutoff (VHS) protein released into the cytoplasm and initiates the degradation of host cell mRNA
- α-Trans-inducing factor (αTIF) is transported to the nucleus

apsid travels to nucleus where viral DNA is released, enters a uclear pore and circularizes

TIF induces the expression of viral alpha genes

- The mRNAs for the alpha genes are translated on ribosomes
- The proteins then enter the nucleus and express the viral beta genes

he beta proteins are involved in degrading cellular chromatin and calizing cellular DNA to the inner side of the nuclear envelope nargination)

ral DNA is replicated as concatemers

amma proteins (structural) are expressed

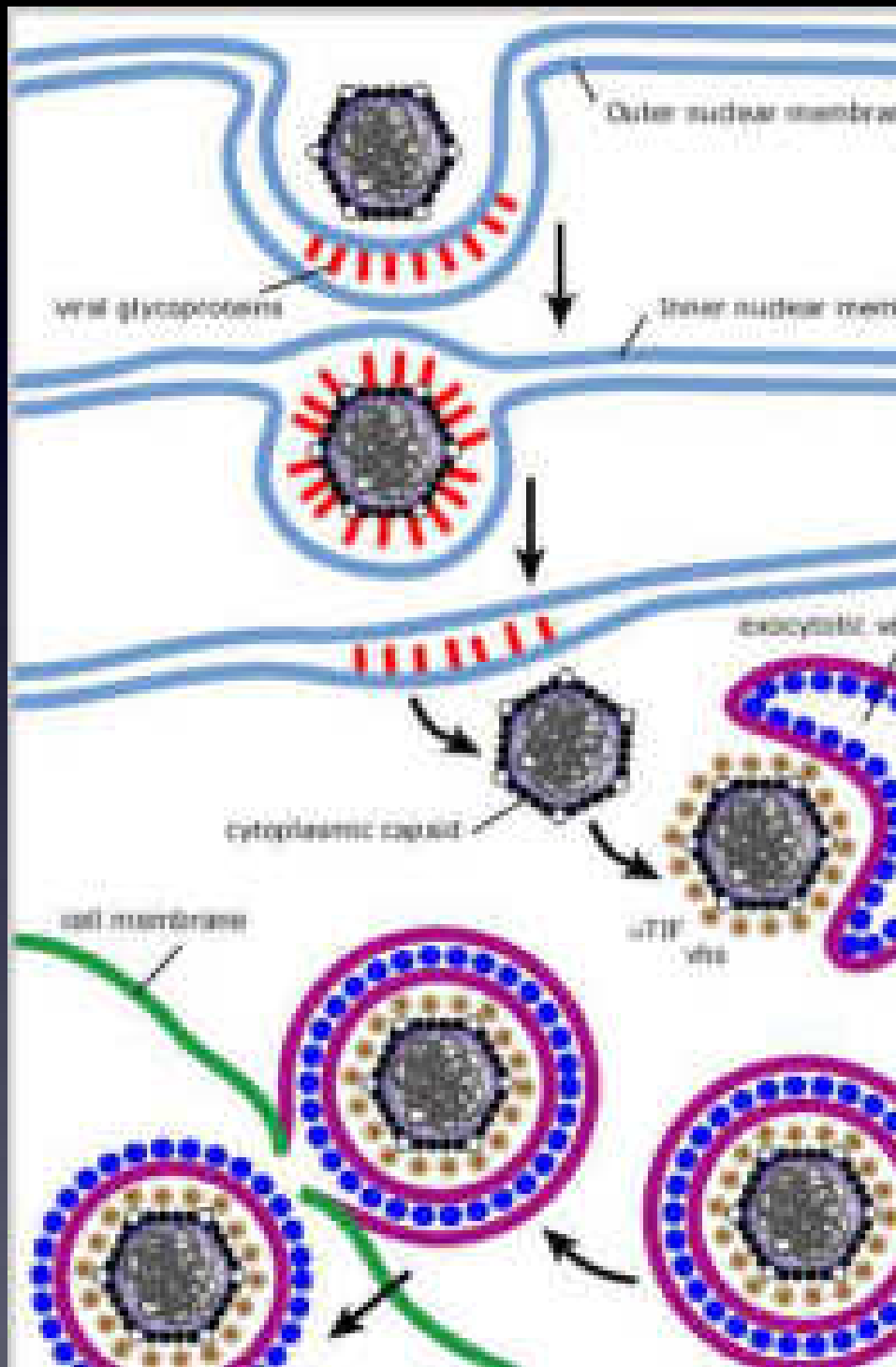
eplication of HSV (cont.)

uclear escape

- Viral proteins induce budding of the capsid through both nuclear membranes
- Thus, capsid escapes into the cytoplasm

iral proteins associate with the ellular vesicles

- These proteins have affinity for the capsid proteins and cause the vesicle to wrap around the virus, providing it with an double-layered envelope
- Virus traverses the ER then Golgi prior to release from the cell
  - The outer membrane fuses with the plasma membrane



lerpes Simplex viruses

wo species

- HSV-1: oropharyngeal sores (children)
- HSV-2: genitalia (young adults)

ighly similar genomes, but distinct

- 150 kb
- 70+ polypeptides

irulence factors

- gC binds complement C3b
- gE is an Fc receptor for IgG

lerpes simplex viruses (cont.)

athology

- Wide cellular tropism
- Most common to dermal tissues (herpetic lesions)
  - Cell fusion followed by cell lysis
  - Inflammatory response
- Transmission
  - Generally through direct contact with person shedding virus
    - Some people shed virus despite absence of lesions
  - Virus enters through mucosal tissues; cannot penetrate healthy skin
- Latent infections
  - Virus sequesters in nerve tissues (immunoprivileged site)
    - HSV-1 in trigeminal ganglia
    - HSV-2 in sacral ganglia
  - Very few genes are expressed by infected cells

lerpes simplex viruses (cont.)

- Clinical conditions
  - Oropharangeal disease
    - Symptoms: fever, vesicular and ulcerative lesions, edema, ginigivostom lymphadenopothy, malaise
    - Recurrence in some people throughout adult life
  - Keratoconjunctivitis
    - Inadvertent self-transmission (aka, autoinoculation) to eye
    - Causes lesions
    - Scarring can cause vision impairment
    - Can lead to an autoimmune response against the eyes
  - Genital herpes
    - Similar lesions and recurrence
    - Complications can occur
      - Transmission to newborn infant

lerpes simplex viruses (cont.)

linical conditions

- Skin infections
  - Documented in laboratory or health care workers with compromised skin
  - Persons with skin diseases can have serious infections
- Encephalitis
  - HSV-1 is most common cause (proximity to brain)
  - High fatality rate in untreated patients (70%)
  - Survival is often accompanied by permanent neurological disorders
- Neonatal herpes
  - Transmission: in utero, during birth, after birth
  - High fatality rate if untreated (50%)
- Immunocompromised hosts
  - Systemic infections

mmunity

mmune response is not sterilizing

- IgG, IgA, IgM
- CTL responses are impaired
  - Viral proteins block MHC class I pathway
    - α47 protein retains class I molecules in the cytoplasm
    - ICP47 protein inhibits peptide translocation into the ER lumen
  - $CD4^+$ T cells act as CTL to kill infected cells
    - Cannot engage ganglia cells

aboratory Diagnosis

ytopathology

- Multinucleated giant cells from skin scrapings

irus isolation

- Immunofluorescence
- Restriction digestion of viral DNA (HSV-1 vs. HSV-2)

CR

- Used for systemic or encephalitic disease

erology

- IgG appears in 4-7 days
- Cannot discriminate HSV-1 from HSV-2

pidemiology

lobal

SV-1

- Most commonly acquired by children
- Most adults are seropositive
- Only a small proportion have recrudescence

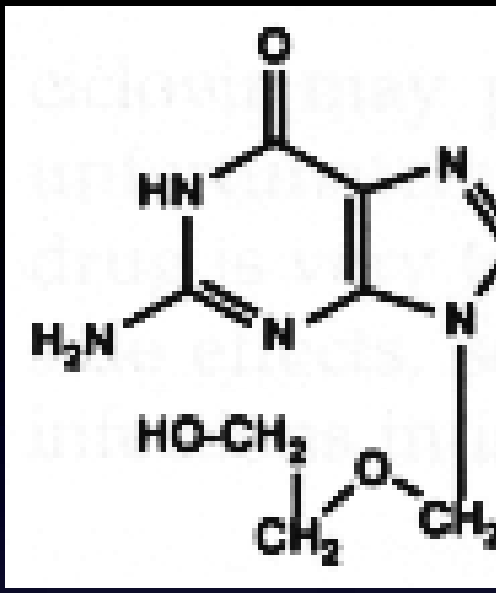
SV-2

- Most commonly acquired by young adults
  - Sexually-transmitted disease
- About 1 in 6 Americans has HSV-2
- Fetal/newborn transmission
- Increased risk for HIV infection

reatment, prevention and control

heomtherapy

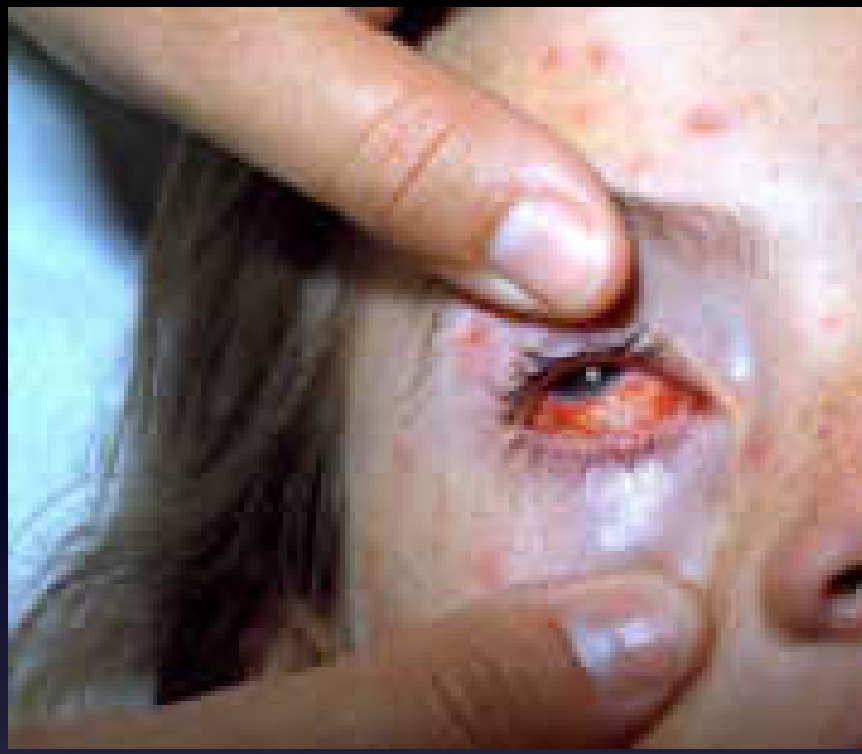
- Acyclovir drug of choice
- Nucleoside analog
  - Phosphorylated by HSV thymidine kinase
  - Then converted into Acy-triphosphate by cellular kinases
  - Incorporated into newly-synthesized HSV DNA and acts as a chain-termin
- Dramatic impact on reduction of transmission and survival of neonatal, visce and encephalitic HSV infections

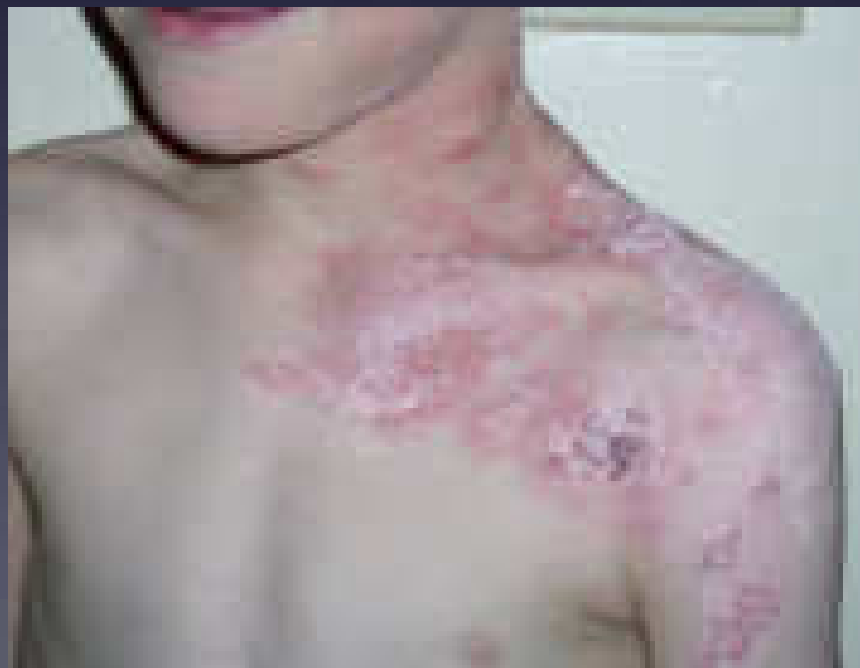


lo vaccine is available

Varicella-Zoster virus

- Varicella ("chickenpox")
- Zoster ("shingles")
- Pathogenesis
  - Varicella
    - Respiratory transmission
    - Replication in regional lymphoid tissue (e.g. mediastinal LN)
    - Viremia
    - Infected mononuclear cells take virus to skin where lesions form
    - Virus sequesters in ganglia
    - Immunity is usually life-long
  - Zoster
    - Recurrence of virus in adults





Varicella-Zoster virus

- Clinical spectrum
  - Almost always apparent
  - 10-21 day incubation
  - Malaise, fever, rash for about 5 days
  - Complications are rare
    - Ocular infections can lead to impaired vision
    - Primary infection as an adult is usually more serious
    - Before vaccine, about 10 people died each year in the U.S.
    - Immunocompromised patients
- Zoster
  - Usually occurs in aged or immunodeficient persons
  - Often starts as lesions on the lower back
  - Painful

Laboratory diagnosis

- Usually not necessary except for immunocompromised
- Virus isolation in human embryonic cells
- Serology

Epidemiology

- Worldwide
- Most children by age 10 (varicella)
- Occasionally in adults (zoster)

Treatment

- No treatment required for healthy persons (except eye infections)
- Immunocompromised patients can get immune globulin (passive immunization)
  - Acyclovir

Vaccination

- Vaccine approved for use in the U.S. in 1995
- Now recommended for children (MMRV tetravalent)
- Vaccination resulted in
  - Fewer hospitalizations
  - Savings of hundreds of millions of dollars in hospital expenses per year

Cytomegalovirus

- Largest genome of the human herpesviruses
- IE promoter is driven by cellular transcription factors

Pathogenesis

- Usually asymptomatic
- Can cause a mononucleosis-like disease
- Viremia leads to wide tissue distribution
- Immunocompromised hosts can have serious pneumonia
- Congenital/perinatal infections
  - About 1% of children in U.S. will be infected with CMV at birth
  - Of these, about 5-10% will have developmental defects

Clinical spectrum

- Usually mild disease
- Immunocompromised can develop systemic disease

Immunity

- IgM, IgG, IgA
- Virus becomes latent with episodes of recurrence

Laboratory diagnosis

- PCR is method of choice
- Virus isolation is slow - two to three weeks before CPE
- Serology is usually not informative

Epidemiology

- Worldwide
- Humans are only known host
- Transmission through close contact (oral/respiratory routes)

Treatment

- Ganaclovir for life-threatening infections

Epstein-Barr virus

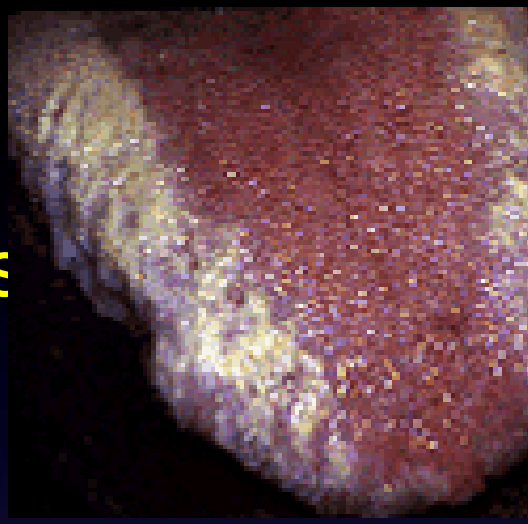
- Around 100 genes
- Targets B cells
  - Can also infect epithelial cells of oropharynx, parotid gland, cervix
- Binds to complement receptor 2 (CR2; aka, CD21)
- Usually becomes latent in the B cell
  - Fewer than 10% of infected cells in vitro release virus
- Can cause transformation
  - Used to make immortalized human B cells that secrete monoclonal antibodies

Pathogenesis

- Transmission through saliva
- Initial replication in epithelial cells
- B cells in lymphoid tissues

Clinical spectrum

- Infectious mononucleosis
  - Lengthy incubation period of up to 50 days
  - Sore throat, fever, malaise,
  - Prolonged recovery
- Oral hairy leukoplakia in HIV patients (epithelial cells)
- Burkitt's lymphoma
  - Tumor of jaw area of lymphoid tissues
  - Most tumors express viral EBNA1
  - Correlates with malaria infections
  - Chromosomal translocations



Laboratory diagnosis

- PCR
- Virus isolation (slow)
- Serology is not useful

Epidemiology

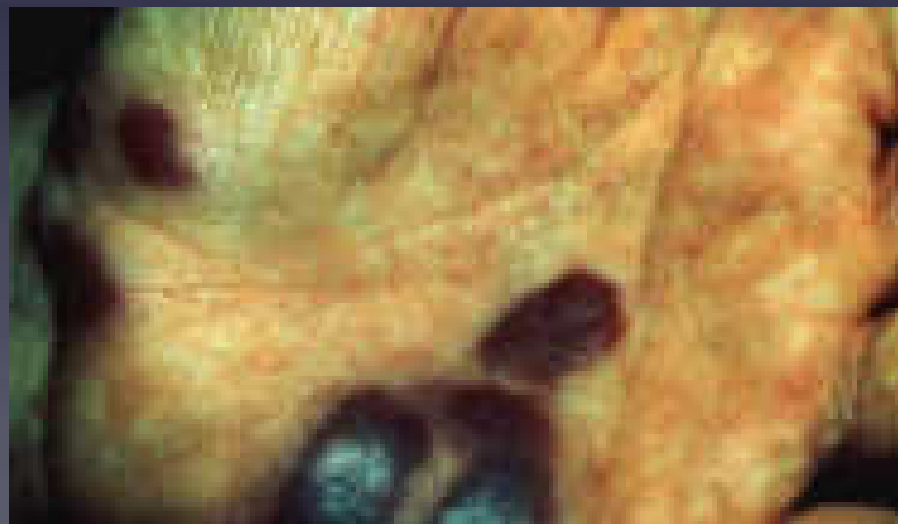
- Worldwide

Prevention and control

- No vaccine available
- Acyclovir has no effect

Other herpesviruses

- HHV-6
  - Infects T cells
  - Causes roseola
  - Only a problem in immunocompromised patients
- HHV-7
  - Infects T cells
  - No known disease
- HHV-8
  - Kaposi's sarcoma virus
    - Before HIV disease, only known to cause disease in men of Mediterranean descent and chemotherapy patients



Herpes B virus

- Formerly known as Herpes simiae
- Officially known as cercopithecine herpesvirus 1
- Almost always fatal in humans
  - Has high propensity for central nervous system and caus substantial damage
  - Survivors usually have neurological disorders
- No effective treatment