Herpesviruses:
Latent Viral Infections

Lecture 1

Human Herpesviruses

<table>
<thead>
<tr>
<th>Herpesvirus</th>
<th>Acute Infection</th>
<th>Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes Simplex Virus, Type I</td>
<td>cold sores</td>
<td>cold sores</td>
</tr>
<tr>
<td>Herpes Simplex Virus, Type II</td>
<td>genital herpes</td>
<td>genital herpes</td>
</tr>
<tr>
<td>Varicella-Zoster Virus (VZV)</td>
<td>chicken pox</td>
<td>shingles</td>
</tr>
<tr>
<td>Epstein-Barr Virus (EBV)</td>
<td>infectious mono</td>
<td>lymphoma/cancer</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>broad spectrum</td>
<td>pneumonia</td>
</tr>
<tr>
<td>Human Herpes Virus 6</td>
<td>Roseola</td>
<td>??</td>
</tr>
<tr>
<td>Human Herpes Virus 7</td>
<td>Roseola</td>
<td>??</td>
</tr>
<tr>
<td>Human Herpes Virus 8</td>
<td>??</td>
<td>Kaposi's sarcoma</td>
</tr>
</tbody>
</table>
Herpesviruses

- dsDNA genome
- Enveloped virus
- gB-gN
- Tegument
- Nucleocapsid (capsid + DNA)

The size and organization of herpes virus genomes. The five human herpesviruses are compared by size in megadaltons, organization of the long unique (UL), short unique (US), and repeat sequences, and the number of isometric forms of the genome.

Sequence of Transcription Events

The sequence of transcription events during herpesvirus infection. The diagram shows the rate of synthesis of immediate, early, and late proteins over time, with lysis occurring after 8 hours.
Herpes Simplex – Type 1

Primary Infection

1. Usually cold sores, sore throat, fever and rarely, encephalitis are also seen.
2. Less frequently found as a genital infection.

Infection and Pathogenesis

- Primary lytic infection of epithelial cells
- Virus infects sensory neurons
  - Latency-associated transcripts (LATs) are the only vmRNA present
- Reactivation: virus travels back to epithelial cells, causing lesions and shedding

The virions are not drawn to scale. In reality, they are much smaller in proportion to the cell.
Herpes Simplex – Type 1

Latent Infection

1. Asymptomatic – no virus produced
2. Viral DNA resides in sensory cells of trigeminal nerve ganglion.
**Herpes Simplex – Type 1**

**Recurrent Infection**
1. Virus replicates and travels down sensory nerve fiber to infect epithelial cells around the nose and mouth
2. Symptoms are usually a milder form of primary infection

**Herpes Simplex – Type 2**

**Primary Infection**
1. Usually vesicular eruptions on the genitalia
2. Spread by sexual contact
3. Affects both sexes
4. Less frequently found as herpes labialis (cold sores)

**Latent Infection**
1. No virus produced
2. Viral DNA resides in sensory cells of sacral ganglion
Herpes Simplex – Type 2

Recurrent Infection

- Milder outbreak
  - generally in same
    - location in genital area
### Infections Associated with Herpes Simplex Viruses

<table>
<thead>
<tr>
<th>Infection</th>
<th>Frequency</th>
<th>Usual Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral herpes</td>
<td>Very common</td>
<td>Resolution</td>
</tr>
<tr>
<td>Genital herpes</td>
<td>Common</td>
<td>Resolution</td>
</tr>
<tr>
<td>Ocular herpes</td>
<td>Common</td>
<td>Resolution, visual impairment</td>
</tr>
<tr>
<td>Neonatal herpes</td>
<td>Very rare</td>
<td>Developmental impairment, death</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Very rare</td>
<td>Neurological impairment, death</td>
</tr>
<tr>
<td>Disseminated herpes</td>
<td>Rare</td>
<td>Resolution or death</td>
</tr>
</tbody>
</table>

### Mechanism of action of acyclovir

![Mechanism of action of acyclovir](image)
Comparison of Intravenous Acyclovir and Placebo Treatment on the Duration of Virus Shedding in Normal Patients with First Episode Genital Herpes

Intravenous Acyclovir n=13
Placebo n=12

Patients with Frequently Recurring Genital Herpes were Treated Chronically with Placebo or Acyclovir Capsules

Acyclovir-Resistant Mutants are seen in Immunocompromised Patients

Resistance is due to mutation in the gene encoding:

- the viral thymidine kinase - the drug is not phosphorylated to the active form
- the viral polymerase - the polymerase no longer efficiently binds the drug
Pritelivir: A New anti-Herpes drug

• Directed against the herpesvirus helicase-primase

Model of the Action of Helicase-Primase Inhibitors
A polymerase (UL30), together with its accessory subunit (UL42), functions in concert with three subunits of the helicase-primase complex (UL5, UL8, and UL52) and the DNA binding protein ICP8 to direct the synthesis of viral DNA. Pritelivir directly interferes with this process by inhibiting the helicase-primase complex and thereby preventing the formation of viral DNA.

Day 6 after infection with HSV-2

Pritelivir Valacyclovir Placebo
Pritelivir reduced the rates of genital HSV shedding and days with lesions in a dose-dependent manner in otherwise healthy men and women with genital herpes (NEJM 2014)

Varicella Zoster

Primary Infection
1. Infection occurs in seasonal epidemics as chicken pox (Varicella)
2. Contracted from another infected individual, usually a child
3. Systemic infection resulting in a generalized, vesicular rash

Varicella

Clinical Features
• Mild prodrome (fever, malaise) for 1-2 days
• Successive crops (2-4 days) of pruritic vesicles
• Generally appear first on head; most concentrated on trunk
• Generally mild in healthy children
Fever

Infection of mucosa of upper respiratory tract

Infection of skin and appearance of vesicular rash

Incubation period

Contagious period

Viral replication in regional lymph node

Viral replication in liver, spleen (T) and other organs

Secondary viremia

Primary viremia

Contagious period

Infection of skin and appearance of vesicular rash

Days
**VZV at the Baker’s**

- **Nov. 27 - Dec 1:** Evan (5 yrs) plays with children at daycare center
- **Dec. 3 (Mon.):** Daycare center reports a child broke out with chickenpox over the weekend
- **Dec 14:** Evan breaks out with chickenpox
- **Dec 28:** Katherine (2 yrs) breaks out with chickenpox - treated with acyclovir

---

**Varicella – United States 1986-1992**

*Cases by Month of Report*

![Varicella Cases Chart](chart.png)
Varicella Complications

- Bacterial infection of lesions
- CNS manifestations
- Pneumonia (rare in children)
- Hospitalization ~ 3 per 1000 cases
- Death ~ 1 per 60,000 cases

Varicella – United States
Age-Specific Annual Incidence

Varicella Case Fatality Rate Healthy Persons
16-month old with *Staphylococcus aureus* infection of Varicella lesions

Varicella Vaccine

<table>
<thead>
<tr>
<th>Composition</th>
<th>Live virus (Oka strain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>95%</td>
</tr>
</tbody>
</table>
| Duration of Immunity | 5 yrs  
                    Probably long-lasting |
| Schedule        | 1 dose (booster likely) |

May administered simultaneously with measles-mumps-rubella (MMR) vaccine
Varicella Vaccine

- Immunization reduces incidence of the most severe disease and hospitalization
- 98% effect in protecting from severe disease
- 70-85% protective against any form of VZV

Annual U.S. Mortality Rates, According to Age, for Deaths with Varicella Listed as the Underlying Cause, 1990-2001
Varicella Zoster

Latent Infection

1. Asymptomatic with no virus or virion proteins produced
2. Viral DNA resides in the cells of dorsal root ganglia

Varicella Zoster

Recurrent Infection

1. Virus travels down the sensory nerve fiber and infects epithelial cells inundated by the fiber
Varicella Zoster

Recurrent Infection (Shingles)

2. Infections are unilateral, painful vesicular eruptions localized to the dermatome, usually in the head or upper trunk

3. Severe systemic infections are observed in immune suppressed individuals

A previously healthy 57-year-old man presented to the emergency department with 5 days of worsening rash on the left side of his forehead (Panels A and B). He had been seen at a clinic 2 days earlier and started on a course of oral acyclovir. The patient came to the emergency department out of concern about crusting and swelling around his left eye. Vesicular, purulent, and crusted lesions consistent with herpes zoster were evident in the ophthalmic distribution of the trigeminal nerve. Ophthalmic examination with direct visualization, slit lamp, and fluorescein staining showed no evidence of accompanying keratitis or uveitis. The results of laboratory tests, including a complete blood count and comprehensive metabolic panel, were all within normal limits. A test for infection with the human immunodeficiency virus was negative. No underlying immunosuppressive illness or ophthalmic involvement was found, and the diagnosis of herpes zoster was made on the basis of findings from the patient's history and physical examination. The patient completed a 10-day course of oral acyclovir, and clindamycin was added to the regimen for suspected bacterial superinfection. Bacterial culture from the lesions grew methicillin-sensitive Staphylococcus aureus. Six weeks after the initial visit, the rash had resolved but postherpetic neuralgia had developed; it improved slightly after treatment with gabapentin.

VZV Vaccine

Immunization of elderly reduces incidence of herpes zoster
**VZIG**

- Varicella-Zoster immune globulin
- Provides passive immunity