Herpesviruses: Latent Viral Infections

Lecture 2

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>
### Epstein-Barr Virus (EBV)

- **Primary infection**
  - Asymptomatic infection
  - **Infectious Mononucleosis**

- **Malignant lymphoproliferative diseases:**
  - Burkitt’s lymphoma
  - Nasopharyngeal carcinoma

### Epidemiology of EBV Infection

- Causes life-long infection
  - Asymptomatic shedding of virus
- Transmission via saliva
- Teenagers and adults at highest risk for infectious mono
- World-wide distribution, no seasonal incidence

### Disease Mechanisms of EBV

- Virus in saliva infects epithelia and spreads to B cells in lymphatics
- Infection promotes growth of B cells
- T cells kill/control B-cell outgrowth, promote latency in B cells
- Severe disease in T-cell deficient patients
EBV in saliva → Epithelial Cells of oropharynx → B-cell Proliferation → T-cell activation → Liver → Lymph node → Spleen → Resolution

Epithelial Cells of oropharynx → Shedding in saliva → Pharyngitis

Heterophile antibody → Atypical lymphocytes (Downey cells) → Swelling

Progression of EBV infection:

- Saliva shedding
- Proliferation
- Saliva
- Epithelial cell
- Lymph node
- Nkp46
- CD8 T cells
- T cells
- B cells
- EBNA 1/2
- LMP 1
- NUEP1
- NUEP2
- T cell activation
- Leukemic lymphoma
- African Bural Lymphoma
Detection of EBV Infection

- Monospot test
detection of heterophile antibodies
  (false neg 5-15%, especially in children)

- Antibody to EBV VCA
  IgM/IgG to viral capsid antigen

Time Course of EBV Infection

- Days after onset of symptoms of primary EBV infection
- Antibody index or EBV log10 copies/mL
- Time Course of EBV Infection

Clinical syndromes:
- Fever
- Lymphadenopathy
- Pharyngitis
- Generalized lymphadenopathy

Laboratory data:
- EBV in oral cells
- EBV in saliva
- EBV in blood
- VCA IgG
- VCA IgM
- EBNA1 IgG

Time:
- Days after onset of symptoms of primary EBV infection
- Months:
  - Days:
    - Day 5
    - Day 10
    - Day 15
    - Day 20
    - Month 1
    - Month 3
    - Month 6
    - Month 12
    - 1 year

SeroLogic data:
- Anti-EBNA
- Anti-EA
- Anti-VCA IgM
- Anti-VCA IgG
Clinical Syndromes of EBV

- Infectious Mononucleosis
- Post-transplant lymphoproliferative disorder (PTLD)
- Hairy Oral Leukoplakia (with AIDS)
- African Burkitt’s Lymphoma (malaria is co-factor)
- Nasopharyngeal carcinoma (China)

Herpesviruses

- Epstein-Barr Virus (EBV)
- Cytomegalovirus (CMV)
Cytomegalovirus (CMV)

- Primary infection
  - asymptomatic infection
  - fetal/neonatal infection can be serious
- Persistent infection/carrier state
  - asymptomatic shedding
  - serious complications in immuno-compromised patients

Outcomes of CMV infections
The outcome of CMV infection depends very heavily on the immune status of the patient.

Epidemiology of CMV Infection

- Causes life-long infection
  - asymptomatic shedding of virus
- Transmission via blood, secretions, including breast milk and semen
- Babies and immunosuppressed individuals are at highest risk for symptomatic and recurrent disease
**Disease Mechanisms of CMV**

- CMV acquired from blood/secretions
- Productive infection of epithelium
- Establishes latency in T-cells, macrophages and other cells
- Suppression of CMI allows recurrence

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**Asymptomatic Shedding of CMV**

<table>
<thead>
<tr>
<th>Source</th>
<th>Neonates</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>0.5 – 2.5%</td>
<td>10 – 29%</td>
<td>0 – 2%</td>
</tr>
<tr>
<td>Oral secretions</td>
<td>0.5 – 2.5%</td>
<td>10 – 29%</td>
<td>0 – 2%</td>
</tr>
<tr>
<td>Cervical secretions</td>
<td>10 – 28%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semen</td>
<td>5 – 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>13 – 27%</td>
<td></td>
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</tbody>
</table>

* Potential for CMV secretion increases in the third trimester of pregnancy

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**Frequency of CMV Disease**

<table>
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<tr>
<th>CMV Disease</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Mononucleosis</td>
<td>10%</td>
</tr>
<tr>
<td>Newborn CMV</td>
<td>0.1%</td>
</tr>
<tr>
<td>AIDS retinitis, pneumonitis</td>
<td>30%</td>
</tr>
<tr>
<td>Post-transplant pneumonia</td>
<td>10%</td>
</tr>
</tbody>
</table>
Laboratory Tests for Diagnosis of CMV Infection

Samples taken for analysis include urine, saliva, blood, bronchoalveolar lavage, and tissue biopsies.

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR</td>
<td>Detection of CMV DNA</td>
</tr>
<tr>
<td>Serology</td>
<td>CMV specific IgM and IgG</td>
</tr>
<tr>
<td>Cytology/Histology*</td>
<td>“Owl eye” inclusion body</td>
</tr>
</tbody>
</table>

Owl's eye nuclei in CMV pneumonia

Ganciclovir

- Activated in CMV-infected cells
- Problem: bone marrow toxicity
New anti-CMV therapeutic!

- Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplant
- Reduced incidence of CMV in transplant patients
- Targets CMV terminase complex

Structure of Cytomegalovirus

Viral DNA, synthesized as a long, multiunit, concatemeric DNA molecule, is packaged into the capsid through a specialized portal protein that replaces one of the pentons in the icosahedral capsid. This packaging is an active process that consumes ATP. When the capsid is full, the terminase complex cleaves the DNA at specific sequences. The process is then repeated for another capsid. The long concatemeric DNA, which contains internal regions recognizable by the terminase complex, can be thought of as a train comprising individual identical coaches, each of which can be released when the terminase complex cleaves the coupling between them.

Letermovir

- CMV replication involves cleaving of concatemeric genomic DNA and packaging of each genome into preformed virus capsids
- The CMV terminase complex (UL56, UL69) performs these sequential events, a viral process not present in uninfected human cells
- Letermovir inhibits the terminase complex by binding to UL56
Epstein-Barr Virus (EBV)
Cytomegalovirus (CMV)
Roseola (HHV-6 and HHV-7)
Kaposi’s Sarcoma (HHV-8)

Herpesviruses

- Epstein-Barr Virus (EBV)
- Cytomegalovirus (CMV)
- Roseola (HHV-6 and HHV-7)
- Kaposi’s Sarcoma (HHV-8)

Roseola (HHV-6 and 7)

- Rapid onset of high fever
- Generalize rash 24-48 hrs later
- T-cells resolve infection
- Latent in T cells
- Recurrence?
Typical HHV6 and HHV7 time course:

- Incubation 4 – 7 days
- Abrupt High Fever 103 – 105°F (2-4 days)
- No Fever, RASH (1-2 days)
- Recovery Without Complications
Epidemiology of Roseola

- Common infection of childhood
  >95% seropositive by age 5

- HHV-6, 7 in infancy is usually symptomatic and often results in medical evaluation.

Cumulative Incidence of Primary HHV-6 Infection

The midpoint between the last negative salivary test for HHV-6 DNA and the first positive test served as the time acquisition.

Roseola

- Resolution of the disease is complete.
  Virus remains latent.

- No rapid diagnostic is currently available

- No specific therapy
Kaposi’s Sarcoma & HHV-8

- Most common neoplasm in AIDS patients
- Multiple types of KS are recognized:
  - Classical, African (endemic)
  - Iatrogenic (post-transplantation)
  - AIDS-related (epidemic)
- Considered a relatively benign disease prior to the AIDS epidemic

Kaposi’s Sarcoma
Kaposi’s Sarcoma

- Spindle-shaped tumor cells
- Neovascularization
- Inflammatory infiltrate

Kaposi’s Sarcoma

- HHV-8 identified in KS lesions
- Sexual transmission
- T-cells likely resolve infection
- Activation of KS during immunosuppression
- In HIV patients, use of antiretroviral drugs reduces/controls KS

Human Herpesviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Approximate Seroprevalence Among Young U.S. Adults (%)</th>
<th>Common Infections</th>
<th>Site of Persistence</th>
<th>Mode of Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>50</td>
<td>Herpes labialis, herpes whitlow, herpetic keratitis, herpes simplex encephalitis</td>
<td>Neuronal cells, especially trigeminal ganglia</td>
<td>Contact with secretions, especially oral</td>
</tr>
<tr>
<td>Type 2</td>
<td>25</td>
<td>Herpes genitalis, herpes proctitis, neonatal herpes</td>
<td>Neuronal cells, especially sacral ganglia</td>
<td>Contact with secretions, especially genital</td>
</tr>
<tr>
<td>Varicella virus</td>
<td>100</td>
<td>Chickenpox, herpes zoster (shingles)</td>
<td>Neuronal cells, especially posterior root ganglia</td>
<td>Contact with infected skin lesions; respiratory route for chickenpox</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>75</td>
<td>Infectious mononucleosis, prolonged fever, malignant macroglobulin</td>
<td>Neuronal cells, especially posterior root ganglia</td>
<td>Contact with oral secretions, blood, or transplant organs</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>50</td>
<td>Erythema infectiosum, prolonged fever, macroglobulin</td>
<td>Neuronal cells, especially anterior horn of spinal cord</td>
<td>Contact with oral secretions, blood, or transplant organs</td>
</tr>
<tr>
<td>Human herpesvirus 6</td>
<td>100</td>
<td>Erythema infectiosum, macroglobulin</td>
<td>Monocytes, macrophages</td>
<td>Contact with oral secretions, blood, or transplant organs</td>
</tr>
<tr>
<td>Human herpesvirus 7</td>
<td>100</td>
<td>Erythema infectiosum, macroglobulin</td>
<td>T lymphocytes</td>
<td>Contact with oral secretions or bone marrow</td>
</tr>
<tr>
<td>Human herpesvirus 8</td>
<td>&lt;10</td>
<td>Kaposi’s sarcoma</td>
<td>Neurasthenia</td>
<td>Contact with bodily secretions</td>
</tr>
</tbody>
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HHV-8 identified in KS lesions

Sexual transmission

T-cells likely resolve infection

Activation of KS during immunosuppression

In HIV patients, use of antiretroviral drugs reduces/controls KS
Why doesn’t the immune system efficiently defend against herpes viruses?