Case Vignette 1

• A 20 yo man presents to clinic with a 2-day history of fevers, malaise, and a painful lump in his right groin. About 6 hours prior to the clinic visit, he noticed multiple painful vesicles in the urethral opening and glans of his penis. He had sexual intercourse (condomless) with a woman he met at a college party about 7 days ago.

• On examination, he has multiple small vesicles, with an erythematous border, on the penile glans and in the urinary meatus. A sample from one of the lesions is sent for HSV PCR testing. He has no prior history of any genital or oral lesions.

• A diagnosis of first-episode genital HSV infection is strongly suspected with a plan to initiate empiric treatment for HSV.
Case Vignette 1 (cont’)

Which one of the following is a recommended treatment for first clinical episode of genital herpes?

A) Acyclovir 400 mg PO TID for 7-10 days
B) Acyclovir 400 mg BID for 3-5 days
C) Valacyclovir 500 mg PO BID for 5-7 days
D) Topical acyclovir applied five times a day for 7-10 days
Learning Objectives

• Describe the epidemiology and clinical presentations of HSV-1 and HSV-2 infections
• Describe the pathogenesis and clinical presentation of other herpes virus infections
• Discuss the treatments for genital herpes and CMV infection
• List the principles of prevention and education in managing genital herpes infection
• Discuss case vignettes
Recap: Herpes Simplex Virus (HSV)

• DNA virus that causes lifelong infection
• Following oral-genital intercourse, HSV may be transported to the trigeminal ganglion
• Following initial genital infection, HSV is transported from the infected epithelial cells along the peripheral nerve axons to the sacral ganglia and paraspinous ganglia
• HSV establishes chronic infection and enters a latent phase
  • Latent infection occurs within sensory or autonomic nerve root ganglia
Human Herpes Viruses (Phylogeny)

Alpha (α) Herpes Virus (Alphaherpesvirinae)
- Replication cycle is short: 8 hours to 18 hours
- Cytopathology: cytolitic
- Host range is broad
- Latency site: sensory ganglia

Beta (β) Herpes Virus (Betaherpesvirinae)
- Replication cycle is long, greater than 24 hours
- Host range is restricted
- Latency site: reticuloendothelial cells, exocrine glands, kidneys, and other tissues

Gamma (γ) Herpes Virus (Gammaherpesvirinae)
- Replication cycle is variable
- Cytopathology: lymphoproliferative
- Host range is very restricted
- Latency site: lymphoid tissue

Herpes Simplex Virus Type 1 (HSV-1)

Herpes Simplex Virus Type 2 (HSV-2)

Varicella-Zoster Virus (VZV) (also known as human herpesvirus 3 [HHV 3])

Human Cytomegalovirus (HCMV) (also known as human herpesvirus 5 [HHV 5])
- Cytopathology: cytomegalic (enlargement of infected cells)

Human Herpesvirus 6 (HHV 6)

Human Herpesvirus 7 (HHV 7)

Epstein-Barr virus (EBV) (also known as human herpesvirus 4 [HHV 4])

Kaposi’s sarcoma-associated herpesvirus (KSHV) (also known as human herpesvirus 8 [HHV 8])

Cytopathology: lymphoproliferative (excessive growth of lymphatic system cells)
Background and Burden of Disease

• Two HSV serotypes: HSV-1 and HSV-2
  • HSV-1 and HSV-2 cause chronic, lifelong viral infections
• HSV-2 causes most cases of recurrent genital herpes
  • Genital herpes is the leading cause of genital ulcer disease worldwide
• Genital herpes is among the most prevalent STI in the US
  • Approximately 50 million people infected
• Approximately 776,000 new cases occur each year
• USA: 15.5% of persons (14 – 49 yo) are infected with HSV-2

CDC. Genital herpes. www.cdc.gov/std/herpes/stdfact-herpes-detailed.htm
Prevalence of HSV Infections

Herpes simplex virus 1 (HSV-1)
- Most commonly acquired by children
- Most adults are seropositive
- Only a small proportion have recrudescence (occasional outbreaks)

Herpes simplex virus 2 (HSV-2)
- More than 80% of persons with HSV-2 are asymptomatic (or unaware of their infection)
- More common in women than in men
- Increased risk of HIV infection
Pathophysiology and Transmission

- HSV infection has 5 key stages:
  - Primary mucocutaneous infection
  - Infection of the ganglia
  - Establishment of latency, reactivation, and recurrent infection

- Occurs through close contact with a person who is shedding virus at a mucosal or epithelial surface, or in genital or oral secretions

- Sexual transmission of HSV-1 and HSV-2 can occur through genital-to-genital, oral-to-genital, or genital-to-oral contact

- Perinatal transmission (mother-to-child) can occur at the time of delivery through direct mucosal or skin contact

- Virus replicates by spreading to adjoining cells and peripheral sensory nerves

- Immune-system responses and emotional and physical stressors can activate the virus
Herpes Simplex Virus Type 1 (HSV-1)

• HSV-1 is commonly acquired during childhood
  • Most children will be infected by 1-2 years old

• HSV-1 infection (herpes labialis, oropharyngeal sores, “cold sores”, or “fever blisters”)

• Primary infection occurs through a break in the mucous membranes of the mouth or throat, via the eye or genitals or directly via minor abrasions in the skin
  • Initial infection is usually asymptomatic, but there may be minor local vesicular lesions
  • Subsequent lifelong latent infection with periodic reactivation
HSV-1 and Risk Factors

WHAT ARE SOME COMMON COLD SORE TRIGGERS?

- Injury to Lips
- Fatigue
- Emotional & Physical Stress
- Sun and Ultraviolet Exposure
- Illness or Fever
- Chapped or Dry Lips

Herpes Simplex Virus

Cold sores

Infected Person

HSV
Herpes Simplex Virus Type 2 (HSV-2)

• Transmitted sexually and perinatally
• Most genital herpes infections are transmitted by persons who are unaware they are infected with HSV-2 (asymptomatic when transmission occurs)
• Efficiency of sexual transmission is greater from men to women than from women to men
• Incubation period after acquisition is 2-12 days (average is 4 days)
• HSV-2 is a strong risk factor for HIV acquisition (approx. 3-fold)
HSV-1 and HSV-2: Signs and Symptoms

• Asymptomatic or mild symptoms

• Symptoms include vesicular lesions around the mouth, genitals or rectum
  • Lesions are generally painless, but may rupture → painful, shallow ulcers that take 2-4 weeks to heal
  • Occurrence of symptoms = outbreak

• Patients may experience prodromal symptoms before ulceration occurs, which can include
  • Flulike symptoms (fever, swollen lymph nodes, HA, and body aches)
  • Mild tingling up to 48 hours before lesion appearance or shooting pain

• The virus can remain dormant indefinitely & the number of outbreaks typically decreases over time
HSV-1 Infection: Clinical Manifestations

• Oropharyngeal disease (a.k.a. herpes labialis)
  • Symptoms: fever, vesicular and ulcerative lesions, gingivostomatitis (“canker sores”, “cold sores”, “fever blisters”), lymphadenopathy, malaise
  • Recurrence in some people throughout adult life

• Keratoconjunctivitis
  • Inadvertent self-transmission (or autoinoculation) to eye
    • Can lead to an autoimmune response against the eyes
    • Causes lesions; scarring can impair vision

• Encephalitis
  • High fatality rate in untreated patients (70%)
  • Symptoms: headaches, odd behavior, dysphagia, hemiparesis, or coma
  • Survival is often accompanied by permanent neurological disorders
HSV-2 Infection: Clinical Manifestations

• Genital herpes
  • Duration of lesions: 2-3 weeks
  • Median recurrence rate = 4 – 6 episodes per year
    • Recurrent episodes: 50% have prodrome of tingling/pain
  • Complications can occur

• Symptoms
  • Systemic symptoms
  • Pain
  • Dysuria

Genital herpes symptoms

- Small blisters that break open and cause painful sores
- Painful during urination
- Pain around genitals
- Itching
- Fatigue

Treatment of herpes outbreak

- Use ice pack to soothe pain
- Use medication
- Apply antiviral cream
- Wear loose cotton clothes
- Don't touch sores
Varicella-Zoster Virus (HHV-3)

- **Varicella virus (“chickenpox”)**
  - Respiratory transmission; normally occurs in childhood (~90%)
  - Replication in regional lymphoid tissue (e.g., mediastinal lymph nodes)
  - Infected mononuclear cells take virus to skin where lesions form
    - Virus sequesters in ganglia
  - Secondary multiplication involves skin and mucosa → vesicles filled with very high titers of infectious virus
  - Immunity is usually life-long

- **Zoster virus (“shingles”)**
  - Recurrence of virus in adults
    - Can occur in 50’s, but could manifest at any age due to stress and weakened immunity
  - Inflammation of ganglia and sensory neurons
Varicella-Zoster Virus (HHV-3): Clinical Conditions

• Varicella virus
  • Almost always apparent
  • 10-21 days incubation
  • Symptoms: malaise, fever, rash for approximately 1 week
  • Complications (rare)
    • Ocular infections → impaired vision
    • Primary infection in adults is more serious
  • Vaccines: Varivax®, ProQuad® (is MMRV)

• Zoster virus
  • Usually occurs in older adults or immunodeficient persons
  • Often starts as lesions on the lower back
  • Painful, may be accompanied with post-herpetic neuralgia
  • Usually resolves without complications
  • Vaccines available (Zostavax®, Shingrix®)
Varicella-Zoster Virus (HHV-3): Clinical Conditions

Varicella (Chickenpox) – ocular involvement

Varicella (Chickenpox)

Herpes-zoster virus (Shingles)
Human Herpes Viruses (Phylogeny)

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**Kaposi’s sarcoma-associated herpesvirus (KSHV) (also known as human herpesvirus 8 [HHV 8])**
Cytomegalovirus (CMV) (HHV-5)

• Majority of population infected by age 40 (>75%)

• Pathogenesis
  • Usually asymptomatic
  • Can cause a mononucleosis-like disease
  • Immunocompromised persons can have serious pneumonia
  • Routes of transmission: sexual, close contacts, transfusion, organ transplant, perinatal

• Clinical spectrum
  • Usually mild disease
  • Congenital infections are sometimes fatal
    • Approximately 1% of children in USA will be infected with CMV at birth → of these, 5-10% will have developmental defects
  • Immunocompromised persons can develop systemic disease
HHV Infections: Antiviral Treatments

- Acyclovir
- Famciclovir
- Cidofovir
- Ganciclovir
- Foscarnet
HSV-Infected Cell

ACV

ACV → ACV-P → ACV-P-P → ACV-P-P-P

Thymidine Kinase

Cellular Kinase

ACV = Acyclovir

HSV TK+
# Acyclic Guanosine Analogues

<table>
<thead>
<tr>
<th>Medication</th>
<th>Bioavailability (F)</th>
<th>ADRs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir (Zovirax®)</td>
<td>5 – 15%</td>
<td>Nausea, diarrhea, HA, fatigue, and/or rash  (possible)</td>
<td>Also available in IV formulation (reserved for serious infections); Topical formulation not effective and usually not recommended; Adjust for renal impairment; Preg. Cat. B</td>
</tr>
<tr>
<td>Valacyclovir (Valtrex®)</td>
<td>15 – 55%</td>
<td></td>
<td>Effective in treating herpes zoster and recurrent genital herpes in immunocompetent adults. Adjust for renal impairment; Preg. Cat. B</td>
</tr>
<tr>
<td>Famciclovir (Famvir®)</td>
<td>~77%</td>
<td></td>
<td>HIV-infected patients: 500 mg orally BID for 5 to 14 days; Adjust for renal impairment; Preg. Cat. B</td>
</tr>
</tbody>
</table>
Topical Antivirals for HSV-1 (a.k.a. Herpes Labialis or “cold sores”)

• Usually self-limiting; rarely requires antiviral therapy

• Topical
  • Docosanol (Abreva®) 10% cream: apply topically to lesions 5 times a day until lesions have healed
  • Acyclovir (Zovirax®) 5% cream: apply topically to lesions 5 times a day for 4 days (for recurrent episodes)
**Systemic Antivirals for HSV-1 (a.k.a. Herpes Labialis or “cold sores”)**

- Valacyclovir (Valtrex®) 2 gm PO Q12h for 1 day (start at the earliest onset of symptoms)
- Famciclovir (Famvir®) 1500 mg PO x1 (start at the earliest onset of symptoms)
HSV-2 (Genital Herpes): Antiviral Medications

• *Systemic* antiviral therapy includes 3 oral medications
  • Acyclovir (Zovirax®)
  • Valacyclovir (Valtrex®)
  • Famciclovir (Famvir®)

• Other indications
  • Herpes labialis (cold sores), herpes zoster (shingles), varicella (chicken pox), Bell’s palsy, eczema herpeticum (pediatrics)

• Topical antiviral treatment is **NOT recommended**
Management of First Episode of Genital Herpes

• Manifestations of first clinical episode may become severe or prolonged

• Antiviral therapy should be used
  • If symptoms <7 days
### CDC – Recommended Regimens for First Episode

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult Dosing and Duration*</th>
</tr>
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<tbody>
<tr>
<td>Acyclovir (Zovirax®)</td>
<td>400 mg PO TID for 7 – 10 days, OR 200 mg PO 5 times daily for 7 – 10 days</td>
</tr>
<tr>
<td>Valacyclovir (Valtrex®)</td>
<td>1 gm PO BID for 7 – 10 days</td>
</tr>
<tr>
<td>Famiciclovir (Famvir®)</td>
<td>250 mg PO TID for 7 – 10 days</td>
</tr>
</tbody>
</table>

*Treatment can be extended if healing is incomplete after 10 days (up to 14 days).
Management of **Recurrent** Episodes of Genital Herpes

• Purpose: to ameliorate/shorten duration of lesions

• Initiate therapy as soon as prodromal symptoms present (preceding outbreak), or within 1 day of lesion onset

• Provide patient with a supply of antiviral medication and instructions to self-initiate therapy immediately when symptoms begin
### CDC – Recommended Regimens for Recurrent Episodes (“Episodic Therapy”)

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</thead>
<tbody>
<tr>
<td>Acyclovir (Zovirax®)</td>
<td>400 mg PO TID for 5 days, OR 800 mg PO BID for 5 days, OR 800 mg PO TID for 2 days</td>
</tr>
<tr>
<td>Valacyclovir (Valtrex®)</td>
<td>500 mg PO BID for 3 days, OR 1 gm PO daily for 5 days</td>
</tr>
<tr>
<td>Famciclovir (Famvir®)</td>
<td>125 mg PO BID for 5 days, OR 1 gm PO BID for 1 day, OR 500 mg PO x1, followed by 250 mg PO BID for 2 days</td>
</tr>
</tbody>
</table>

2015 STD Treatment Guidelines: Genital Herpes
Chronic **Suppressive** Therapy for Genital Herpes

- **Purpose:** to reduce frequency of recurrences and protect at-risk partners
  - *Having > 6 recurrences per year*
  - Reduce frequency of recurrences by ~70-85%
- Reduces but does not eliminate subclinical viral shedding
- Periodically (e.g., once a year), reassess need for continued suppressive therapy
## CDC – Recommended Regimens for Chronic Suppressive Therapy (up to 1 year)

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</tr>
<tr>
<td>Famciclovir (Famvir®)</td>
<td>250 mg PO BID</td>
</tr>
</tbody>
</table>

*HIV patients: Valacyclovir 500 mg PO BID

2015 STD Treatment Guidelines: Genital Herpes
Severe HSV Disease

• IV acyclovir should be provided for patients with severe disease or complications requiring hospitalization

• Encephalitis, Shingles, mucosal & cutaneous
  • Acyclovir 5-10 mg/kg IV every 8 hours
  • Treatment duration will vary depending on diagnosis and immune status
  • Given via IV infusion over one hour
CMV – Treatments

- Ganciclovir (Cytovene®)
- Valganciclovir (Valcyte®)
- Foscarnet (Foscavir®)
- Cidofovir (Vistide®)
CMV Infection: Antiviral Treatments

**Ganciclovir (Cytovene®)**

- Indications: CMV retinitis and prevention of CMV infection in transplant patients (heart, kidney, kidney-pancreas)
- Dosage and duration – vary depending on diagnosis
  - Induction phase (5 mg/kg IV Q12H), then maintenance phase
- Monitoring
  - CBC, BUN/Scr

**Valganciclovir (Valcyte®)**

- Indications: CMV retinitis and prevention of CMV infection in transplant patients (heart, kidney, kidney-pancreas)
- Dosage and duration – vary depending on diagnosis
  - Induction phase (900 mg PO BID), then maintenance phase
- Monitoring
  - CBC, BUN/Scr
Foscarnet (Foscavir®)

- Indication: CMV infection, Herpes simplex, mucocutaneous (acyclovir-resistant), and Varicella-zoster infection (acyclovir-resistant)
- Dosage and duration – vary depending on diagnosis
  - There is an induction phase, followed by a maintenance phase
  - Administer hydration fluid (750-1000 mL) subsequent to all foscarnet doses
- Monitoring: CBC, electrolytes, BUN/SCr, QTc prolongation

Cidofovir (Vistide®)

- Indication: CMV retinitis
- Dosage
  - Induction: 5 mg/kg IV Qweek x2 wks, then maintenance dose x3-6 mos.
  - Give saline hydration & probenecid before and after each infusion
- Monitoring: CBC, BUN/SCr
Prevention
Patient Counseling and Education

• Goals of counseling
  • Help patients cope with the infection
  • Prevent sexual and perinatal transmission
• Counsel initially at first visit
• Provide education on chronic aspects may be beneficial after acute illness subsides
• HSV-infected persons may express anxiety about genital herpes that does not reflect the actual clinical severity of their disease
Patient Counseling and Education (cont’)

• Counseling should include:
  • Natural history of the infection
  • Treatment options
  • Transmission and prevention issues
  • Neonatal HSV prevention issues

• Emphasize potential for recurrent episodes, asymptomatic viral shedding, and sexual transmission
Strategies to Prevent HSV-2 Transmission

• Inform current and future sex partners about genital herpes diagnosis

• Abstain from sexual activity with uninfected partners when lesions or prodrome present (during outbreaks)

• Use safe sex practices
  • Correct and consistent use of latex condoms might reduce the risk of HSV transmission

• Use chronic suppressive therapy (i.e., acyclovir or valacyclovir)
Case Vignettes
Case Vignette 1

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Case Vignette 2

• AP, 38-year-old woman with recurrent genital herpes, presents for evaluation of her fourth genital herpes episode in 3 years. She finds these episodes annoying and bothersome.

• The physician treated AP for her current outbreak until lesions resolved.

• Though the episodes are not too frequent, she is interested in reducing the duration and severity of genital lesions, but does not want to take medications daily for prolonged periods.

• The physician asks you the following:
Summary – Key Takeaways

• Topical treatment recommended for herpes labialis ("cold sores"), which is mainly caused by HSV-1
  • Docosanol (Abreva®) or acyclovir (Zovirax®) topical

• Genital herpes is a chronic viral infection caused by HSV-2, and is characterized by periods of latency punctuated by periods of viral shedding

• Antiviral therapy (acyclovir, valacyclovir, or famciclovir) recommended to treat genital herpes symptoms ("episodic therapy") and to prevent recurrences plus reduce viral shedding and transmission ("suppressive therapy")

• Oral acyclovir is preferred for treatment of genital herpes in pregnancy

• Ganciclovir and valganciclovir are preferred treatments for CMV infections
Resources

- Herpes-American Sexual Health Association
- University of Washington Virology Research Clinic
- Centers for Disease Control and Prevention—Genital Herpes