Genital Herpes

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Genital Herpes: A challenging STI

- Genital herpes is caused by HSV-1 or HSV-2
  - HSV-1 and HSV-2 have similar but unique natural history, sites of infection, disease presentation
- Chronic, no cure
  - Management of symptoms
  - Transmission concerns
- Often asymptomatic/subclinical
  - Requires reliance on blood tests to determine infection
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Epidemiology
Epidemiology and Burden: HSV-related GUD in 2016

Looker et al, BMJ Global Health 2020

HSV-2: 178 million people
HSV-1: 9 million people
8 billion days with HSV-related GUD in 2016
492 million people worldwide are infected with HSV-2 (2016)

<table>
<thead>
<tr>
<th>Region</th>
<th>Female Prevalence</th>
<th>Female Number</th>
<th>Male Prevalence</th>
<th>Male Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Region</td>
<td>43.9%</td>
<td>102.9M</td>
<td>25.4%</td>
<td>59.3 M</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>24.0%</td>
<td>57.7 M</td>
<td>11.6%</td>
<td>28.0 M</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>7.6%</td>
<td>12.8 M</td>
<td>2.8%</td>
<td>5.1 M</td>
</tr>
<tr>
<td>European Region</td>
<td>10.7%</td>
<td>22.2 M</td>
<td>5.3%</td>
<td>11.1 M</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>9.6%</td>
<td>48.4 M</td>
<td>7.2%</td>
<td>38.5 M</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>14.6%</td>
<td>65.5 M</td>
<td>7.1%</td>
<td>36.0 M</td>
</tr>
</tbody>
</table>

James et al, Bull World Health Organization 2020
Trends in HSV seroprevalence in the United States, 1999–2015

Overall US HSV seroprevalence:
• HSV-1: 47.8%
• HSV-2: 11.9%
Genital Herpes Epidemiology: United States

Among U.S. 18-49 year olds in 2018

- 18.6 million prevalent infections
  - 2/3 of prevalent infections were in 35-49 year olds
    - Women account for 65% of prevalent infections
  - 572,000 new infections/year
  - Equal numbers in men and women

Estimates do not include genital HSV-1 infection
Would add millions of additional prevalent infections

Spicknall et al STD 2021;48 (4): 260-65
Figure 4. Trends in age-adjusted prevalence of herpes simplex virus type 2 among persons aged 14–49, for the total population and by race and Hispanic origin: United States, 1999–2000 through 2015–2016

1Significant decreasing linear trend over time, p < 0.05.
NOTES: Age adjusted by the direct method to the 2000 U.S. Census population, using age groups 14–19, 20–29, 30–39, and 40–49 years. Total population includes all race and Hispanic-origin groups including those not shown separately. Data for the Asian subpopulation are only available since 2011, so this subpopulation is not shown separately, but included in the total population. Access data table for Figure 4 at: https://www.cdc.gov/nchs/datadownload/dbs04_table.pdf#.
HSV-1 Seroprevalence: USA NHANES 1976-2010

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Microbiology
HSV-1 and HSV-2

• HSV-1 and HSV-2 are closely related viruses
• Large double-stranded DNA viruses
• Do not integrate into the host genome
• Well adapted to the host – express many immune evasion genes
• Cause a chronic infection – the body is not able to clear the virus
• Reactivation and symptoms may occur across the lifespan

Centers for Disease Control and Prevention Public Health Image Library. Dr. Fred Murphy & Sylvia Whitfield, 1975.
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Pathogenesis
HSV pathogenesis

- **Primary infection:**
  - Inoculation/epithelial replication
  - Retrograde transport to sensory ganglia
  - Ganglionic replication, inter-neuronal spread
  - Acute anterograde transport to periphery
  - Immune control
- **Latency in sensory neurons**
  - Establishment, maintenance, reactivation
  - Immune control
- **Lytic replication, axon, across “gap” to keratinocyte**
  - Immune control
- **Epithelial replication, shedding, ± lesions, ± transmission**
  - Immune control
HSV-2 and Genital Inflammation

- HSV-2 infection is associated with 2-3 fold increased risk of HIV infection
- Chronic inflammation in genital track of people with HSV infection
- Persistent CD4+ cells which express HIV co-receptors

Zhu et al, Nat Med, 2009
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Transmission
Transmission

• Contact with virus-containing secretions
  - Viral shedding may be subclinical/asymptomatic

• Occurs with skin-to-skin contact
  - No transmission via fomites
  - Genital-genital
  - Anal-genital
  - Oral-genital (HSV-1)

• Entry through microabrasions in the skin/mucosa
### Transmission of Genital HSV-2 Infection

<table>
<thead>
<tr>
<th>Source Partner</th>
<th>Exposed Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>♀</strong></td>
<td><strong>♂</strong></td>
</tr>
<tr>
<td>Virus in genital secretions:</td>
<td>Cultures:</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Itching:</td>
<td>Genital lesions:</td>
</tr>
<tr>
<td>•</td>
<td>• • • • • • •</td>
</tr>
<tr>
<td>Sexual Activity</td>
<td>HSV-2 serology:</td>
</tr>
<tr>
<td><img src="heart" alt="Heart" /> <img src="heart" alt="Heart" /> <img src="heart" alt="Heart" /></td>
<td>- +</td>
</tr>
</tbody>
</table>

**HSV DNA/ml**

- **10⁸**
- **10⁷**
- **10⁶**
- **10⁵**
- **10⁴**

**Date (March)**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 29 |
|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|

*Note: The table indicates the presence (+) or absence (-) of various symptoms and conditions.*
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Manifestations
Genital herpes is the leading cause of genital ulcer disease
Genital Herpes Classification

- First episode genital herpes
  - Primary
    • No antibody to either HSV-1 or HSV-2
  - Nonprimary first episode
    • Antibody to HSV-1 or HSV-2 present during first outbreak

- Recurrent genital herpes
Primary Genital Herpes

- Sexual contact
  - Lesions noted
  - Provider contacted
  - New lesion formation common
  - Lesions start to heal
  - Symptoms gone unless lesions irritated
  - Symptoms healed

Primary Genital Herpes

• Multiple genital lesions, severe pain may be present
• Autonomic nervous system involvement is possible
  - urinary retention
• Systemic symptoms such as fever, chills, myalgias, headache may be present
First episode Genital HSV

• ~Half have true primary infection with either HSV-1 or HSV-2
  - Increasing % of HSV-1
    • Women & MSM at higher risk

  - ~25% are HSV-2 seropositive

• Remainder are HSV-1 seropositive and have acquired HSV-2
Recurrent Genital Herpes

- Generally milder and limited to genital area
- Prodrome is frequent (mild tingling to sacral neuralgia)
- 90% with HSV-2 will recur in year following primary:
  - ~4 episodes/ year
- On average, less frequent recurrences with genital HSV-1
  - Median 1 episode/year in year following primary
- Less frequent recurrences over time
Genital Ulcer Disease: Differential Diagnosis

• Infectious
  - Syphilis
  - MPOX
  - Lymphogranuloma venereum (chlamydia)
  - Chancroid

• Non-infectious
  - Behcet’s disease
  - Fixed drug eruption
  - Dermatitis (candida/contact)
  - Inflammatory bowel disease
The following slides will contain photos of genital herpes for educational purposes.
Pustules
Ulcers
Dry Crust
Genital Herpes Presentations

• Proctitis may occur with/without lesions
  - Symptoms: fever, pain, discharge, tenesmus
  - HSV is a leading cause of infectious proctitis among MSM

• Urethritis can be caused by HSV-1/HSV-2
  - Differential diagnosis: gonococcal/non-gonococcal urethritis
Genital Herpes Presentations

- Neonatal HSV is a rare complication of genital HSV infection, in which virus is transmitted when genital shedding occurs during birth process, highest risk when HSV is acquired in pregnancy
- Fulminant hepatitis/disseminated disease
  - Risk factors: Pregnancy, primary infection
- Recurrent meningitis (Mollaret’s meningitis)
- More severe, refractory genital herpes in people with immunocompromising conditions
  - HIV with low CD4 counts
    - Acyclovir resistant HSV may develop
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Diagnosis
The Clinical Spectrum of HSV-2

- Asymptomatic: 20%
- Recognized Symptomatic: 20%
- Undiagnosed: 60%
Diagnostic Method Must Be Tailored to Clinical Presentation

- **Asymptomatic**: 20%
- **Recognized symptomatic**: 20%
- **Undiagnosed**: 60%

Serologic diagnosis: Type specific serology

Virologic Diagnosis: Culture, PCR
Virologic Diagnosis

• When a genital ulcer is present, virologic diagnosis should always be attempted
  - HSV PCR is preferred
    • More sensitive than viral culture
    • Both PCR and culture can differentiate between HSV-1 and HSV-2, which may have important counseling messages for patient
    • Many FDA approved PCR assays are available
Virologic Diagnosis

• Swab the base of the ulcer
  - virus is present in epithelial cells
  - unroof vesicles/pustules if present

• Dry crust phase may be associated with negative PCR
  - viral shedding has ceased at this stage of infection
HSV Serology: Type Specific Antibody Testing

Glycoprotein gG tests IgG tests
- Western blot
- gG ELISA
- gG-membrane tests
- gG immunoblot

• Differentiate between HSV-1 and HSV-2

• IgM Testing is not useful and not recommended
2021 CDC STI Treatment Guidelines: When to consider testing for HSV antibodies

- Recurrent or atypical genital symptoms with negative PCR/culture result
- Clinical diagnosis of genital herpes without laboratory confirmation
- Partner with genital herpes

- Persons presenting for STI evaluation
  - Consider screening for symptoms of genital herpes, serologic screening if symptoms
Diagnosis of genital herpes: Pitfalls

• FDA-approved serologic assays differentiate between HSV-1 and HSV-2 (glycoprotein G)
  - Most are enzyme immunoassay (EIA) or chemiluminescence assay (CLIA)
  
  - Retrospective study among 864 patients with HSV EIA followed by UW WB
    • Issues: HSV-1: **70.2% sensitive**, 91.6% specific
      HSV-2: 91.9% sensitive, **57.4% specific**
      Dependent upon index value and HSV-1 serostatus

<table>
<thead>
<tr>
<th>EIA Index value</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1-2.9</td>
<td>39.8%</td>
</tr>
<tr>
<td>≥3.0</td>
<td>78.6%</td>
</tr>
</tbody>
</table>

False positives more likely at low index values and in HSV-1 seropositive persons
2021 CDC STI Guidelines: How to test for HSV antibodies

- Serologic two-step testing for HSV-2 is recommended
  - poor specificity of EIA assays with low index values (<3.0)
  - Serologic diagnosis of HSV2 requires confirmation
    - (different HSV-2 antigen)
    - BioKit – NOT AVAILABLE
    - UW Western Blot:
      - Serologic testing 12 wks after suspected recent acquisition
      - IgM not recommended

If confirmatory tests are unavailable, patients should be counseled about the limitations of available testing before obtaining serologic tests, and health care providers should be aware that false-positive results occur.
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Treatment
Treatment of genital herpes in 2021

- 2021 CDC STI Treatment Guidelines
  - Acyclovir
  - Valacyclovir (prodrug of acyclovir)
  - Famciclovir (prodrug of penciclovir)
- General principle: Suppressive vs. Episodic therapy
- Mechanism of action: Guanosine nucleoside analogues
  - Activated by viral thymidine kinase
  - Only active in cells with HSV present
  - Low toxicity, well tolerated
  - Low risk of resistance
Antiviral Interventions for HSV

• Beneficial
  - Oral antiviral therapy in first episodes
    • If suspected, start treatment; don’t wait
  - Oral antiviral therapy at a start of recurrence
  - Daily antiviral therapy in people with high rates of recurrence
  - Oral antiviral therapy suppresses shedding by 70-80%
  - Daily antiviral therapy to prevent transmission
# Summary of Herpes Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>First episode</th>
<th>Episodic</th>
<th>Suppressive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treat 7-10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACV</td>
<td>400 mg TID</td>
<td>400 mg TID x 5 days–or-800 BID x 5 days or TID x 2 day</td>
<td>400 mg BID</td>
</tr>
<tr>
<td>VAL</td>
<td>1 gm BID</td>
<td>500 mg BID x 3-5 days –or-1 gm x 5 days</td>
<td>500 mg QD –or-1 gm QD (if &gt;9 recurrences/year)</td>
</tr>
<tr>
<td>FAM</td>
<td>250 mg TID</td>
<td>125 mg BID x 5 days –or-1 gm BID x 1 day –or-500 mg x 1 then 250 BID x 2 day</td>
<td>250 BID</td>
</tr>
</tbody>
</table>

*Please refer to 2021 CDC STI Treatment Guidelines for dosages for PWH, pregnant people.*

Workowski et al MMWR 2021, 2021 CDC STI Treatment Guidelines
Optimizing suppressive Rx

• Severity of disease and patient preference the most important
  - All patients should be aware of possibility for suppressive therapy

• Long-term safety data for acyclovir and valacyclovir, famciclovir
  - No evidence of emergence of resistant strains in immunocompetent persons

• Long-term: discuss discontinuation after 1 yr

• Short-term suppressive therapy: job interview, vacation

• Discuss discordant relationships and prevention
Optimizing episodic HSV Rx

• Clinically significant benefit (20 - 30%)
  - Decreased duration with therapy

• Self -initiation of therapy important
  - Medication needs to be available to patient
    • Prescription on hand
Suppression for genital HSV-1: Principles*

- Offer for those with frequent outbreaks
- Shared decision making:
  - Discuss for those who are concerned about transmission
- Explain that we don’t have data for prevention of HSV-1 transmission
  - Benefit is unknown
- Explain that shedding is less frequent in genital HSV-1
- Discuss how concerned they are for transmission to partners
  - Does your genital herpes diagnosis cause distress?

*Similar points for asymptomatic HSV-2 infection
Valacyclovir vs. Acyclovir vs. Famciclovir

- Few head to head studies
- Valacyclovir has higher bioavailability
- Can be dosed less often than acyclovir with higher AUC
  - Hard to maintain 5x/day dosing for ACV
  - Famciclovir inferior to VAL in suppression of shedding and time to first recurrence
  - Equivalent for suppression of recurrences
Antivirals: Prevention of Transmission


1498 Monogamous, HSV-2 discordant couples

48% risk reduction: not U=U

Data extrapolated to MSM, WSW
HSV-2 prevention/treatment strategies

Antiviral agents
- Acyclovir, valacyclovir, famciclovir
  - Episodic: Decrease length of GUD recurrence
  - Suppressive: Daily antiviral therapy decreases risk of GUD and transmission (50%) among HSV-2 discordant couples without HIV infection in North America

Condoms
- 30% decreased risk of transmission if used all of the time

Male circumcision
- Decreased risk of HSV-2 acquisition in men
- Decreased risk of GUD in men and female partners

Disclosure of serostatus
- May decrease risk of transmission ~50%
- Requires knowledge of serostatus

Vaccines
- Several candidates in pipeline for therapeutic vaccine, stay tuned

Martin Arch Int Med 2009; Corey NEJM 2004; Wald JID 2007; Tobian NEJM 2009; Mehta AIDS 2012
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Screening
Serologic Screening for Genital Herpes Infection
US Preventive Services Task Force
Reaffirmation Recommendation Statement

EVIDENCE ASSESSMENT The USPSTF concludes with moderate certainty that the harms outweigh the benefits for population-based screening for genital HSV infection in asymptomatic adolescents and adults, including pregnant persons.

RECOMMENDATION The USPSTF recommends against routine serologic screening for genital HSV infection in asymptomatic adolescents and adults, including pregnant persons. (D recommendation)


US Preventive Services Task Force, JAMA 2023
Screening

• Screening for genital herpes *symptoms* recommended for people presenting for STI screen
  - Consider performing serologic testing if symptoms are elicited

• If better serologic tests were widely available, we could revisit utility for screening
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