Genital Ulcer Diseases – Does It Hurt?

- Painful
  - Chancroid
  - Genital herpes simplex

- Painless
  - Syphilis
  - Lymphogranuloma venereum
  - Granuloma inguinale

HSV-2: “Primer”

- Highly prevalent globally:
  - 22% of sexually active adults in United States
  - 60% of HIV-negative men who have sex with men (MSM) in Peru
  - 50% to 70% of HIV-negative women in southern Africa
  - >80% in HIV-infected men and women globally

- Most common cause of genital ulcer disease (GUD) globally

- Up to 90% of HSV-2-seropositive persons do not report prior GUD; but after counseling, most recognize genital herpes

- Majority shed HSV-2 in the genital tract, even if previously unrecognized genital lesions are infectious
Outbreak Presenting as Erythema

Outbreak Presenting as an Excoriation

Outbreak Presenting on the Buttock

Photo courtesy of Jeffrey Gilbert, MD.
Meatal HSV outbreak

Up to 70% of Transmission May Occur During Asymptomatic Viral Shedding

9.7% of patients infected their partner (14/144)

Transmission frequently occurs between outbreaks

Transmission During Asymptomatic Viral Shedding

Transmission During Symptomatic Outbreaks


References:
5. Data on File, GlaxoSmithKline.

Asymptomatic Viral Shedding Is Common and Can Occur Frequently

<table>
<thead>
<tr>
<th>Asymptomatic Shedding*</th>
<th>Via Culture†</th>
<th>Via PCR†</th>
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<tbody>
<tr>
<td>% of patients with ≥1 day1,4</td>
<td>51% - 61%</td>
<td>72% - 88%</td>
</tr>
<tr>
<td>% of days1,4,5</td>
<td>2.0% - 6.6%</td>
<td>6% - 27%</td>
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Patients with genital herpes shed virus an estimated 30 to 100 days during the year without having symptoms4,5


Patients Cannot Predict When They Will Shed Virus Asymptomatically

50% of asymptomatic shedding episodes occurred more than 7 days from a lesion

32% of days on which shedding was detected were asymptomatic rather than symptomatic

110 women followed for a median of 105 days, swabbed vulva, cervix, and rectum daily for culture
Interactions: HSV-2 and HIV

Effect of HIV on HSV-2
• Alters clinical presentation & frequency of HSV-2 shedding
• Longer duration of lesions (CD4 <200)
• ↑ HSV-2 acquisition & transmission

Effect of HSV-2 on HIV
• ↑ HIV acquisition
• ↑ HIV levels in plasma & genital tract
• ↑ HIV transmission

Epidemiologic Symmetry between HSV-2 and HIV*
• HSV-2+ adults are at twice the risk of acquiring HIV
• 60-80% of those with HIV are infected with HSV-2
• HSV infection alters course of HIV-1
  • HSV-2 reactivation increases HIV plasma levels
  • HIV-1 infection changes natural history of HSV-2
• HSV-2+ / HIV+ have more severe outbreaks and more frequent episodes of herpetic viral shedding

*No antiviral has been approved to improve the course of HIV disease or reduce the risk of acquiring HIV

Laboratory Methods for Diagnosing Genital Herpes
Type-Specific Serology to Detect HSV-2 Antibody

Western Blot
Not commercially available but can be sent to Univ. of Washington

FDA approved IgG type-specific tests include:
HerpeSelect® ELISA HSV-2 or HSV-1
HerpeSelect® Immunoblot for HSV-2 and HSV-1
HerpeSelect® Express (rapid test)
bioMérieux HSV-2 Rapid Test
Captia HSV-2 Select Test

Treatment of Genital Herpes
Initial episode

Recommended Regimens*
• Acyclovir 400 mg orally three times a day for 7–10 days
  OR
• Acyclovir 200 mg orally five times a day for 7–10 days
  OR
• Famciclovir 250 mg orally three times a day for 7–10 days
  OR
• Valacyclovir 1 g orally twice a day for 7–10 days

*Treatment can be extended if healing is incomplete after 10 days of therapy.
### HSV Episodic Treatment of Recurrences

- **Recommended Regimens**
  - Acyclovir 400 mg orally three times a day for 5 days
  - Acyclovir 800 mg orally twice a day for 5 days
  - Acyclovir 800 mg orally three times a day for 2 days
  - Famciclovir 125 mg orally twice daily for 5 days
  - Famciclovir 1000 mg orally twice daily for 1 day
  - Famciclovir 500 mg once, followed by 250 mg twice daily for 2 days
  - Valacyclovir 500 mg orally twice a day for 3 days
  - Valacyclovir 1 g orally once a day for 5 days

### HSV Suppressive Therapy

- **Recommended Regimens**
  - Acyclovir 400 mg orally twice a day
  - Famciclovir 250 mg orally twice a day
  - Valacyclovir 500 mg orally once a day
  - Valacyclovir 1 g orally once a day

*Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥10 episodes per year).*

### HSV and HIV Treatment

**Recommended Regimens for Daily Suppressive Therapy in Persons with HIV**

- Acyclovir 400-800 mg orally twice to three times a day
- Famciclovir 500 mg orally twice a day
- Valacyclovir 500 mg orally twice a day

**Recommended Regimens for Episodic Infection in Persons with HIV**

- Acyclovir 400 mg orally three times a day for 5–10 days
- Famciclovir 500 mg orally twice a day for 5–10 days
- Valacyclovir 1 g orally twice a day for 5–10 days

### Chancroid

- **Etiology** – *Haemophilus ducreyi*
- **Incubation** – 2-10 days
- **Symptoms:**
  - Painful ulceration (can have multiple lesions)
  - Nonindurated, “dirty” base, surrounding erythema
  - Uni- or bilateral inguinal lymphadenopathy
  - Bubo formation (suppurative lymphadenitis)
  - May rupture and form draining sinus tract
Treatment of Chancroid

Recommended regimens

- Azithromycin 1 g PO single dose
- Ceftriaxone 250 mg IM single dose
- Ciprofloxacin 500 mg PO BID for 3d
- Erythromycin 500 mg PO QID for 7d
Lymphogranuloma Venereum (LGV)
• *Chlamydia trachomatis* infection (“*L*” types)
• Classic presentation: inguinal lymphadenopathy (buboes) and genital ulcers
• Endemic in Southeast Asia, Caribbean and Africa
• Rare in industrialized countries

LGV Stages – Primary and Secondary
• Occurs in 3 stages
  • Majority in the primary and secondary stages may go undetected.
  ✓ **Primary stage**
    ◦ Painless herpetiform ulceration at the site of inoculation.
  ✓ **Secondary stage**
    ◦ Men - painful inguinal lymphadenitis (usually unilateral) and constitutional symptoms
    ◦ Lymphatic drainage through the inguinal lymph nodes
    ◦ Homosexual men & women - perirectal and pelvic LN involvement
      • In women, lymphatic spread from the cervix and posterior vaginal wall
    ◦ Early – “fleshy” nodes show diffuse reticulosis; later - suppurative granulomatous lymphadenitis and perilymphadenitis with node matting
      ◦ Nodes coalesce to form stellate abscesses.
    ◦ Histologically, abscesses are nearly diagnostic
      • Clinical appearance may be similar to cat scratch fever and mycobacterial granulomatous infections.
Tertiary LGV

- Characterized by proctocolitis.
  - Lymphorrhoids or perianal condylomata may be observed on rectal examination.
    - Similar to hemorrhoids; result of an obstruction of lymphatics
  - Rectal examination: granular mucosa and palpable, enlarged lymph nodes under the bowel wall. Stricture usually occurs 2-5 cm above the anocutaneous margin, and digital examination above the stricture may reveal smooth healthy mucosa
  - In very late stages, fibrosis and granulomas are characteristic
    - In women, esthiomene (“eating away”) occurs, which results in hypertrophic, chronic granulomatous enlargement of the vulva and subsequent ulceration. This may not appear for 1-20 years after the primary infection.
    - In men, elephantiasis of the genitalia can occur.
Lymphogranuloma Venereum Among Men Who Have Sex with Men — Netherlands, 2003–2004

Lymphogranuloma venereum (LGV) is a sexually transmitted disease (STD) caused by a variety of the bacteria Chlamydia trachomatis that typically occurs in the United States and other sub-Saharan countries, the prevalence of LGV is rapidly rising, particularly among men who have sex with men (MSM). In a study of 8,000 men who had sex with men, 12% of men had LGV.

Table 1. Results of laboratory tests for Chlamydia trachomatis, IV, and other causes of sexually transmitted diseases (STDs) in 20 patients in the lymphogranuloma venereum (LGV) study.

<table>
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Resurgence of Lymphogranuloma Venereum in Western Europe: An Outbreak of Chlamydia trachomatis Serovar L2 Proctitis in The Netherlands among Men Who Have Sex with Men

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Background: Lymphogranuloma venereum (LGV) is a sexually transmitted disease (STD) caused by Chlamydia trachomatis. LGV has been thought to be eradicated in Western Europe, but recent reports have suggested that LGV is reemerging in several countries.

Figure 2. Endoscopic view of the rectum in 2 patients with acute proctitis due to lymphogranuloma venereum. Left: Proctoscopy showing a large ulcer with some penile scarring in the distal part of the rectum. The center of the ulcer shows a diabet after the patch injury. Right: Proctoscopy showing a small circular ulceration with shiny demarcation and normal intervening mucosa.

CDC: 2004 – D. Olofsson • Niesaprodutt et al.

9/29/2014
LGV Proctocolitis

Pictures courtesy of Kimberly Workowski, MD

Lymphogranuloma Venereum

- Recommended Regimen
  - Doxycycline 100 mg PO BID for 21d

- Alternative Regimen
  - Erythromycin 500 mg PO QID for 21d

Granuloma Inguinale (Donovanosis)

- Rare in U.S., endemic in India, New Guinea, Caribbean, parts of Africa and Australia
- Caused by Klebsiella (Calymmatobacterium) granulomatis
- Indolent painless genital ulcers with granulation tissue; “pseudobubo”
- Incubation: 2 weeks to 3 months
- Dx: crush or touch prep ⇒ Donovan bodies (intracellular bipolar staining in macrophages)
Tissue smear stained by rapid Giemsa (RapiDiff) technique showing numerous Donovan bodies in a monocyte.

Tissue smear stained by rapid Giemsa (RapiDiff) technique showing numerous Donovan bodies in monocytes including some in intracytoplasmic cysts (arrow).

Granuloma Inguinale - Treatment

Recommended Regimen
- **Doxycycline**: 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed

Alternative Regimens
- **Azithromycin**: 1 g orally once per week for at least 3 weeks and until all lesions have completely healed
  OR
- **Ciprofloxacin**: 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed
  OR
- **Erythromycin**: base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed
  OR
- **Trimethoprim-sulfamethoxazole**: one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed

The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens can be considered if improvement is not evident within the first few days of therapy.