Genital Ulcer Disease: Herpes, Syphilis, Chancroid, LGV, Donovonosis

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Genital Ulcer Disease
Case 1

• 22 year old woman
• History
  – 4 days increasing vulvar pain and sores
  – 2 days soreness in the groin, headache, fever
  – Regular unprotected sex only with her boyfriend
  – Their relationship began 3 months ago
• Examination
  – Acutely ill, in tears
  – Oral temperature 38.2 C
  – Bilateral inguinal lymphadenopathy, firm, tender
  – And…
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Genital Ulcer Disease
Case 1

• What is your diagnosis?
• What laboratory tests are indicated?
• Treatment?
• What advice about her boyfriend?
Genital Ulcer Disease
Case 1

• What is your diagnosis?
  – Primary genital herpes

• What laboratory tests are indicated?
  – Culture or PCR for HSV, if available
  – Consider baseline HSV serology
  – Routine STD screening (chlamydia, gonorrhea, syphilis and HIV serologies)

• Treatment?
  – Acyclovir, valacyclovir, or famciclovir

• What advice about her boyfriend?
  – Examine and counsel
  – Type specific HSV serology, if available
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Genital Ulcer Disease
Case 2

• 32 year old man

• History
  – “A sore on my penis” for 1 week and “another sore this morning”; uncomfortable but not overtly painful; no other symptoms
  – Relationships
    • Married, last sex 4 days ago
    • Second regular partner (“small house”), last sex 2 days ago
    • Sex with a third woman he met in a bar “a month ago”
  – HIV negative by history, last tested “a couple of years ago”

• Examination
  – Generally healthy appearance
  – No lymphadenopathy or skin rash
  – And…
Genital Ulcer Disease
Case 2

• What is your diagnosis?
• What laboratory tests are indicated?
• Treatment?
• What advice about his sex partner?
Genital Ulcer Disease
Case 2

• What is your diagnosis?
  – Primary syphilis

• What laboratory tests are indicated?
  – Darkfield microscopy
  – Syphilis serology (EIA, RPR as available)
  – PCR or culture for HSV (if available)
  – ± HSV serology (consider, if available)
  – HIV serology (POSITIVE)
Darkfield Microscopy
Fluorescent Monoclonal Antibody (experimental)
Rapid Plasma Reagin (RPR)

• Syphilis Enzyme Immunoassay (EIA); rapid test if available
• Consider TPPA or other specific test
Genital Ulcer Disease
Case 2

• What is your diagnosis?
• What laboratory tests are indicated?
• Treatment?
• How should he be advised about his sex partners and how should they be managed?
Genital Ulcer Disease
Case 2

• Treatment?
  – Benzathine penicillin G 2.4 million units IM

• How should he be advised about his sex partners and how should they be managed?
  – Advise all three be notified and treated with benzathine penicillin G 2.4 MU IM
  – Recommend HIV testing
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Genital Ulcer Disease
Case 3

• 50 year old married engineer with Boeing Corporation

• History
  – Enlarging painful penile sore for 10 days, onset 3 days after last sexual exposure
  – Painful swelling in groin for 3 days
  – Recently returned to Seattle from business in Kenya, where he had sex several times with a Kenyan flight attendant
  – No other symptoms

• Examination
  – General healthy appearance
  – Afebrile
  – And...
Genital Ulcer Disease
Case 3

• What is your diagnosis?
• What laboratory tests are indicated?
• Treatment?
• What advice about his sex partner?
Genital Ulcer Disease
Case 3

• What is your diagnosis?
  – Chancroid

• What laboratory tests are indicated?
  – Gram stained smear is a consideration
  – Culture (or ideally PCR) for *Haemophilis ducreyi*, if available
  – Darkfield microscopy
  – Syphilis serology (EIA, RPR, etc)
  – HSV culture or PCR, if available
  – HIV serology

• Treatment?
  – Ceftriaxone 250 mg IM
  – (Ciprofloxacin 250 mg BID x 5 days)
  – Needle aspiration of fluctuant lymph nodes

• What advice about sex partners?
  – Notify and advise his African partner
    • HIV positive
  – Had not resumed sex with his wife; no steps taken
Genital Ulcers – Algorithm (WHO)

Patient complains of a genital sore or ulcer

Take history and examine

Only vesicles present? NO

TREAT FOR HSV2
TREAT FOR SYphilis IF INDICATED¹

Sore or ulcer present? NO

TREAT FOR SYphilis
AND CHANCROID
TREAT FOR HSV2²

YES

Educate and counsel
Promote condom use and provide condoms
Offer HIV counselling and testing if both facilities are available
Genital Ulcers – Algorithm (WHO)

1 Indications for syphilis treatment:
   - RPR positive; and
   - Patient has not been treated for syphilis recently.
2 Treat for HS/2 where prevalence is 30% or higher, or adapt to local conditions.
Etiology of Genital Ulcer Disease

- 516 GUD patients from STD Clinics in 10 of 11 U.S. cities w/ highest syphilis rates
- Excluded patients with typical herpes
- PCR for HSV, *T. pallidum, H. ducreyi*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV</td>
<td>333</td>
<td>64.5%</td>
</tr>
<tr>
<td>Syphilis</td>
<td>64</td>
<td>12.4%</td>
</tr>
<tr>
<td>HSV + Syphilis</td>
<td>13</td>
<td>2.5%</td>
</tr>
<tr>
<td>Chancroid</td>
<td>16</td>
<td>3.1%</td>
</tr>
<tr>
<td>PCR negative</td>
<td>116</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

Mertz K et al, *JID* 1998;178:1795-8
Clinical Diagnosis of Genital Ulcer Disease

• N = 446; microbiologic or virologic diagnosis made in 220 (49%)

• Sensitivity of classical clinical appearance was poor (31-35%) for herpes, syphilis, and chancroid

• Specificity was good for syphilis (98%), high PPV

• Specificity only 94% for HSV and chancroid, low PPV

• Conclusion: Classic chancre reliably indicates syphilis, but is insensitive; otherwise, clinical diagnosis is unreliable → lab tests essential

DiCarlo RP, Martin DH. CID 1997;25:299-300
# Etiology of GUD in Africa

<table>
<thead>
<tr>
<th>Study subjects</th>
<th>HSV (%)</th>
<th>HIV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maseru, Lesotho</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>Rakai, Uganda</td>
<td>43</td>
<td>NG</td>
</tr>
<tr>
<td>Carletonville, South Africa</td>
<td>13</td>
<td>56</td>
</tr>
<tr>
<td>Capetown, South Africa</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Abidjan, Ivory Coast</td>
<td>27</td>
<td>NG</td>
</tr>
<tr>
<td>Pune, India</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Chiang Mai, Thailand</td>
<td>82</td>
<td>46</td>
</tr>
<tr>
<td>Phonm Penh, Cambodia</td>
<td>79</td>
<td>NG</td>
</tr>
<tr>
<td>Kingston, Jamaica</td>
<td>52</td>
<td>22</td>
</tr>
</tbody>
</table>

NG = not given.
Genital Herpes Trends in Africa

Harare and Durban: Percentage genital herpes of new STI diagnoses
Durban-2 and Johannesburg: HSV prevalence among GUD cases
Rwanda: HSV prevalence among HIV+ GUD cases

# Etiology of GUD in Botswana, 1993-2002


<table>
<thead>
<tr>
<th>Agent or type of infection, by population</th>
<th>1993 Prevalence, % (range)</th>
<th>2002 Prevalence, % (range)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and women with genital ulcer disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>37.0</td>
<td>73.5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Syphilis (RPR and TPHA)</td>
<td>51.9</td>
<td>5.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><em>Haemophilus ducreyi</em></td>
<td>33.2 (32.4, 33.7)</td>
<td>0.6 (0.3–0.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><em>Treponema pallidum</em></td>
<td>1.1 (−0.5–1.2)</td>
<td>0.5 (−1.8–1.3)</td>
<td>.99</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>35.1 (32.5–38.6)</td>
<td>60.5 (58.4–62.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
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Genital Ulcer Disease
Case 4

• 28 year old woman
• History
  – Asymptomatic
  – Seeking care as contact of a partner with gonorrhea
• Examination
  – General healthy appearance
  – Afebrile
  – And…
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Genital Ulcer Disease
Case 4

• What is your diagnosis?
• What laboratory tests are indicated?
• Treatment?
The rest of the story
- Lesion shown to patient with mirror
- “I never saw anything like that before”
- However, on palpation she perceived a region of painless swelling in about the same spot...
- and realized that she had noticed the same thing 3-4 times in the preceding 1-2 years; “I just never thought much about it”
Genital Ulcer Disease
Case 4

• What is your diagnosis?
  – Recurrent genital herpes

• What laboratory tests are indicated?
  – PCR or culture for HSV
  – Type specific HSV serology (predict positive for HSV-2 antibody)
  – Syphilis serology

• Treatment?
  – Discuss/offer suppressive antiviral therapy
    • Acyclovir
    • Valacyclovir
    • Famciclovir

• What advice about sex partners?
  – Notify and advise
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Genital Ulcer Disease
Case 5

• 30 year old man
• History
  – Sore on penis, no other symptoms
  – Vague historian; duration uncertain, probably 1-2 weeks
  – Sexual history: evasive
• Examination
  – General healthy appearance
  – Bilateral nontender inguinal lymphadenopathy
  – And…
• What is your diagnosis?
• What laboratory tests are indicated?
• Treatment?
Genital Ulcer Disease
Case 5

• Laboratory results
  – RPR positive
  – Darkfield positive for motile spirochetes AND
  – Positive culture for HSV-2

• Diagnosis
  – Primary syphilis
  – Genital herpes
Herpes Simplex Virus

- Mucocutaneous infection, retrograde infection along sensory nerves, latent infection in cranial nerve or dorsal spinal ganglia, mucocutaneous recurrences
- HSV-1
  - Mostly orolabial (cold sores, fever blisters)
  - 20-30% of initial genital herpes
- HSV-2
  - Almost entirely genital; oral infection rare
  - >90% of recurrent genital herpes
Relative Risk of HIV Acquisition in HSV-2 Positive Versus HSV-2 Negative Persons

Freeman EE et al, *AIDS* 2006;20:73-83
Genital Herpes and HIV Transmission

- HSV-2 infection, with or without symptoms, is the single most important STD in the U.S. and worldwide in enhancing HIV transmission efficiency
- HSV-2 seropositive persons have 2-5 fold increased risk of acquiring HIV if sexually exposed
- HSV-1 has no apparent influence on HIV risk
- Persons with HIV and symptomatic HSV-2 apparently are more efficient HIV transmitters
- Potential role for HSV-2 screening in persons with HIV or at risk
- Unfortunately, treatment of HSV-2 infected persons apparently does not alter HIV acquisition rate
Clinical Spectrum of Genital Herpes

• First episode infection
  – Primary: First infection with HSV-1 or -2 (20%)
  – Nonprimary first-episode: Prior infection with the opposite HSV type (40%)
  – First clinical episode of longstanding infection (40%)
• Recurrent infection: Second or subsequent recognized outbreak
• Subclinical infection: ~60-90% of infections
  – Truly asymptomatic
  – Unrecognized
Clinical Manifestations of Genital Herpes

• Initial and primary infection
  - Vesiculopustular lesions (bilateral)
  - Cervicitis, urethritis
  - Lymphadenopathy
  - Neuropathic manifestations
  - Systemic inflammation (fever, etc)

• Recurrent outbreaks
  - Unilateral lesions
  - Nonspecific symptoms (discharge, dysuria, etc)
  - Neuropathic prodrome
  - Lymphadenopathy and systemic symptoms rare

• Common misdiagnoses
  - Vulvovaginal candidiasis and other vaginal infections
  - Syphilis, chancroid
  - Urinary tract infection
Complications of HSV-2 Genital Infection

- Localized neuropathic manifestations
- Meningitis (isolated, recurrent)
- Erythema multiforme, Stevens Johnson syndrome
- Perinatal and maternal morbidity
  - Neonatal herpes
  - Cesarean section
- Nongenital autoinoculation syndromes (conjunctivitis, keratitis, whitlow)
- Chronic localized disease in immunodeficient patients (especially HIV/AIDS)
- Enhanced HIV transmission
- Psychosocial impact (cultural variability)
Recurrence Rate After Initial Genital Herpes

- Mean recurrence rate in first year after initial genital HSV-2 infection (N = 457, median FU 391 days)
  - Men 5.2 episodes/yr
  - Women 4.0 episodes/yr
- >6 recurrences in first year 38%
- >10 recurrences in first year 20%

- Rate gradually declines over several years
- Recurrence after initial genital HSV-1 (N = 83)
  - Mean recurrences 1.3 yr 1, 0.7 yr 2 & beyond
  - 38% had no recurrences
What Triggers Recurrent Outbreaks?

- Oral HSV-1
  - Other infections ("cold sore", "fever blister")
  - Actinic/ultraviolet injury
  - Other local trauma (e.g., surgery)
- Genital HSV-2
  - *No clearly documented triggers*
  - No good data support stress, diet, menstruation, sex, etc, despite anecdotal reports and strongly held beliefs to the contrary
Subclinical Viral Shedding in Genital Herpes: Summary

- Present 1-10% of asymptomatic days in persons who have recurrent herpes due to HSV-2 (PCR 5-30%)
- Max frequency (5-10% of days) (PCR 20-30%) in first year, then declines; but probably 2-3% of days (PCR 3-5%) for many years
- >90% of persons with HSV-2 have Asx shedding
- Similar frequency in persons with and without Sx
- Most episodes symptomatic but unrecognized
- Accounts for most transmission
- Relatively uncommon in genital HSV-1 infection
Treatment of Genital Herpes

Initial Episode

- Acyclovir 400 mg *tid* x 7-10 d
- Famciclovir 250 mg *tid* x 7-10 d
- Valacyclovir 1.0 g *bid* x 7-10 d
Episodic Treatment of Recurrences

- Acyclovir 400 mg *tid* (or 200 mg 5x/d) for 3 days
- Valacyclovir 500 mg *bid* for 3 days
- Famciclovir 125 mg *bid* for 3 days
- Still shorter courses may be effective
  - Acyclovir 800 mg *tid* for 2 days (shown effective by randomized controlled trial)
  - Valacyclovir 2.0 g twice, 12 hr apart (effective for recurrent orolabial herpes)
Treatment of Genital Herpes

Suppressive Therapy

- Acyclovir 400 mg $bid$
- Valacyclovir 500-1000 mg $qd$
- Famciclovir 250 mg $bid$
Time to Acquisition of either HSV-1 or HSV-2 in Susceptible Partners

Placebo (n=741)
Valaciclovir (n=743)

P = 0.012
HR 0.45 (0.24-0.84)

Topical Acyclovir or Penciclovir for Genital Herpes

- Ineffective; do not use
What About Managing Stress, Diet, “Natural” Remedies, etc?

• No clear biological basis
• Attempts to reduce stress usually are fruitless
• Avoid “obvious” triggers that are easily identified and avoided
• Rely on antiviral therapy
Syphilis
The Basics

• History
  – The first recognized STD
  – A scourge of Europe and all colonized lands, 15th - 19th centuries
  – Profound influence on human history; the AIDS of its day
• Etiology: *Treponema pallidum*
  – Not cultivable
  – An ancient organism; related pathogens are found in most mammals, many reptiles and amphibians
• Pathogenesis: Similar to tuberculosis
  – Slowly replicating intracellular pathogen
  – Initial benign infection with silent bacteremia, seeding multiple organs
  – Reactivation (aging, immune dysfunction) characterized by destructive granulomatous inflammation
  – Cell mediated immunity contains infection
Syphilis
Clinical Stages and Manifestations

- **Primary syphilis**
  - Incubation period 3 - 6 weeks
  - Chancre: Mucocutaneous ulcer, usually single, indurated, painless, sexually exposed site
  - Regional lymphadenopathy
  - Silent bacteremia

- **Secondary syphilis**
  - Onset 6 - 12 weeks
  - Papulosquamous rash, often including palms, soles
  - Mucous membranes (mucous patches, condylomata lata)
  - Generalized lymphadenopathy
  - Any organ system
  - Neurological involvement usually present (usually asymptomatic)
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Syphilis
Clinical Stages and Manifestations

• Tertiary syphilis
  – 1 - 30 years or more
  – Destructive lesions of brain, heart, any organ
• Latent syphilis
  – Asymptomatic, positive blood test
• Congenital
  – In utero transmission
  – Fetal death
  – Wide range of clinical manifestations in survivors, from asymptomatic to life threatening or disabling
  – Worldwide disability and death may match or exceed that of perinatally acquired HIV/AIDS
Syphilis
Diagnosis

• Direct microscopy
  – Primary
  – Secondary (mucosal lesions)

• Serology: Nontreponemal and treponemal tests analogous to HIV
  ELISA (screening) and Western blot (confirmatory)
  – Nontreponemal tests (VDRL, RPR, etc)
    • Titre correlated with disease activity; becomes negative with
      treatment or spontaneous resolution
    • Confirm with treponemal test, when available
    • Screening, assess response to treatment
  – Treponemal tests (FTA-ABS, TPPA, MHA-TP etc)
    • Usually positive for life
    • Unaffected by treatment
    • Confirms nontreponemal test
## Syphilis Treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line treatment</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Second line treatment</td>
<td>Doxycycline</td>
</tr>
<tr>
<td></td>
<td>Azithromycin?</td>
</tr>
<tr>
<td>Primary, secondary</td>
<td>Benzathine penicillin G 2.4 million U IM, single dose</td>
</tr>
<tr>
<td>Late (&gt;1 yr) or tertiary</td>
<td>BPG x 3</td>
</tr>
<tr>
<td>Symptomatic neurosyphilis</td>
<td>IV penicillin G</td>
</tr>
<tr>
<td>Can’t give penicillin?</td>
<td></td>
</tr>
<tr>
<td>- Primary, secondary</td>
<td>Doxycycline (Azithromycin?)</td>
</tr>
<tr>
<td>- Tertiary, esp. neuro</td>
<td>Penicillin! Or ceftriaxone</td>
</tr>
</tbody>
</table>
Syphilis
Treatment with Azithromycin?

- Promising characteristics
  - Active against *T. pallidum*
  - Favorable pharmacology: Oral, prolonged activity (single dose)
  - Animal model data
- Clinical trials: 2.0 g single dose effective against primary and secondary syphilis
  - Uncontrolled early studies
  - Two large RCTs (versus BPG)
- Evolving resistance (ribosomal RNA mechanism)
  - First documented for erythromycin 1970s
  - Rapid selection and spread in some populations (San Francisco, Dublin)
  - Apparently uncommon in Madagascar; no other geographic data exist
- Use with caution if at all, IF local resistance not documented, and ONLY IF CLOSE FOLLOW-UP CAN BE ASSURED
Chancroid

- History
  - One of the 5 original venereal diseases
  - “Soft chancre”
  - Historic confusion with herpes?
- Etiology: *Haemophilus ducreyi*
- Epidemiology
  - Historic association with commercial sex workers (perhaps related to infrequency of asymptomatic infection)
  - The first STD associated with enhanced HIV transmission
Chancroid

- Clinical manifestations
  - Localized genital ulceration
  - Regional lymphadenopathy (bubo)
  - No systemic illness
  - Asymptomatic carriage appears to be uncommon

- Treatment
  - Erythromycin 500 mg qid x 5 - 14 days
  - Azithromycin 1.0 g PO single dose
  - Ceftriaxone 250 mg IM single dose
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Lymphogranuloma Venereum

- **History:** One of the 5 original venereal diseases
- **Etiology:** *Chlamydia trachomatis* (L1, L2, L3)
- **Epidemiology**
  - Rare in industrialized countries
  - Recent reappearance (?) in MSM, transmitted directly from rectum to rectum by hands, sex toys, etc
  - Remains relatively common in some developing countries
- **Clinical manifestations**
  - Genital ulcer (small, evanescent)
  - Urethritis, cervicitis (probable)
  - Regional lymphadenopathy, bubo
  - Rectal infection
  - Lymphatic obstruction, genital elephantiasis
- **Treatment:** Doxycyline, Azithromycin, or Erythromycin x 14-21 days
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Donovanosis (Granuloma Inguinale)

• History
  – One of the 5 original venereal diseases
• Etiology: *Calymmatobacterium (Klebsiella) granulomatis*
• Epidemiology
  – Rare everywhere; pockets in South Asia, Australia
  – Sexual transmission uncertain
• Clinical manifestations
  – Indolent genital ulcer, hypertrophic tissue
  – Local extension mimics lymphadenopathy
  – Occasional distant metastasis (osteomyelitis)
• Treatment
  – Doxycyline 100 mg PO bid x 14-28 days (?)
  – Co-trimoxazole 800/160 mg bid x 14-28 days (?)
Genital Ulcers – Algorithm (WHO)

Patient complains of a genital sore or ulcer

Take history and examine

Only vesicles present?

TREAT FOR HSV2
TREAT FOR SYPHILIS IF INDICATED

Sore or ulcer present?

TREAT FOR SYPHILIS AND CHANCROID
TREAT FOR HSV2

Educate and counsel
Promote condom use and provide condoms
Offer HIV counselling and testing if both facilities are available
Genital Ulcers – Algorithm (WHO)

1. Indications for syphilis treatment:
   - RPR positive; and
   - Patient has not been treated for syphilis recently.

2. Treat for HS/2 where prevalence is 30% or higher, or adapt to local conditions.
Thank You!

CONTACT

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