

30 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD



Sexually Transmitted Infections: Genital Ulcer Diseases

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

INCLUDED PHOTOS

Please note: all photos are freely available from the following website unless otherwise noted:

<http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm>

GENITAL ULCER DISEASES (GUD)

- Syphilis (*Treponema pallidum*)
- HSV-2
- HSV-1
- Chancroid (*Haemophilus ducreyi*)
- Lymphogranuloma venereum (LGV) (*Chlamydia trachomatis*)
- Granuloma inguinale (Donovanosis) (*Klebsiella granulomatis*)

PAIN AND GUD

Which ulcers are PAINFUL?

- HSV
- Chancroid

Which ulcers are PAINLESS?

- Syphilis*
- LGV (but lymphadenopathy is PAINFUL)
- Granuloma inguinale

* >30% of patients have **multiple painful lesions**

"KEY WORDS" IN GUD

- SYPHILIS: Single, **painless** ulcer or chancre at the inoculation site with heaped-up borders & clean base; painless bilateral LAD (>30% of patients have **multiple painful lesions**)
- HSV: multiple, **painful**, superficial, vesicular or ulcerative lesions with erythematous base

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"KEY WORDS" IN GUD CONTINUED

- CHANCROID: painful, indurated, 'ragged' genital ulcers & tender **suppurative inguinal adenopathy** (50%); **kissing lesions** on thigh
- GI: **Painless**, progressive (destructive), "**serpiginous**" ulcerative lesions, without regional lymphadenopathy; beefy red with white border & highly vascular
- LGV: short-lived **painless** genital ulcer accompanied by **painful suppurative inguinal lymphadenopathy**; "**groove sign**"

GUD: CONCEPTS TO KNOW

- Organisms that cause disease
- Geographic distribution for less common agents
- Diagnostic approach(es)
- Therapeutic approach(es)

QUESTION #1

A 35-year-old woman presents with a painless ulcer on her vulva and one on her soft palate following unprotected vaginal and receptive oral sex 3 weeks earlier. She has no other symptoms.

Examination reveals the two ulcers with heaped-up borders and a clean base.

QUESTION #1

Which of the following diagnostic tests is **inappropriate** to obtain?

- A. Serum RPR
- B. Serum VDRL
- C. Serum treponemal EIA
- D. Darkfield microscopy on a specimen obtained from the oral ulcer
- E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

SYPHILIS: TAKE-HOME POINTS

- Neurological and ocular manifestations may occur during any stage of syphilis
- Both treponemal and non-treponemal tests may be nonreactive in primary syphilis but they are almost ALWAYS reactive in secondary and early latent syphilis (remember prozone reaction for non-treponemal test mainly in secondary syphilis)
- Treponemal tests are almost always reactive in late syphilis (once positive always positive) irrespective

EARLY SYPHILIS: CLINICAL MANIFESTATIONS

- Incubation ~3 weeks
- Primary: chancre; LAD; resolves 3-6 wks
- Secondary: **Systemic symptoms**: low-grade fever, malaise, sore throat, adenopathy
 - RASH: evanescent, copper-colored, macular (dry) rash; followed by a red papular eruption (involving palms and soles); mucosal lesions (gray plaques or ulcers); **condyloma lata**- wart-like lesions that develop in moist areas
 - Other manifestations: uveitis, patchy alopecia, **hepatitis** (mild elevation of aminotransferases with **disproportionately high alkaline phosphatase**), gastritis, periostitis, glomerulonephritis



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NEUROLOGICAL MANIFESTATIONS OF SYPHILIS

- Can occur during any stage of infection
- Can be either asymptomatic or symptomatic
- **Symptomatic Early Neurosyphilis**
 - Occurs within the **first year** after infection
 - **Mainly among HIV+ persons**
 - **Presents as meningitis** (headache; photophobia; cranial nerve abnormalities; ocular symptoms)
- **Symptomatic Late Neurosyphilis (tertiary syphilis)**
 - Usually occurs ~10 years **AFTER** primary infection
 - Divided into 2 categories:
 - Meningovascular
 - Parenchymatous

LATE NEUROSYPHILIS (TERTIARY)

Meningovascular

- Endarteritis of the small blood vessels of the meninges, brain, and spinal cord.
- Typical clinical manifestations include **strokes (middle cerebral artery distribution is classic)** and seizures

Parenchymatous

- Due to actual destruction of nerve cells
- **Tabes Dorsalis:** shooting pains, ataxia, cranial nerve abnormalities; optic atrophy
- **General Paresis:** dementia, psychosis, slurring speech; Argyll Robertson pupil

OTHER TERTIARY MANIFESTATIONS

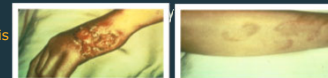
Cardiovascular

- 15-30 years after latency
- Men 3X> women
- Aortic aneurysm; aortic insufficiency; coronary artery stenosis; myocarditis

Late benign syphilis

- 'Gummas'
- Granulomatous process involving skin, cartilage, bone (less commonly in viscera, mucosa, eyes, brain)

Up to 30% of patients with cardiovascular and late benign syphilis will have concomitant neurological involvement- perform CSF exam!



SYPHILIS: EYES AND EARS

Eyes

- Ocular manifestation may occur during any stage and may involve any portion of the eye
 - Uveitis & neuroretinitis: mainly secondary stage
 - Interstitial keratitis: occurs in both congenital (typically at age 5-20; 80% bilateral) and acquired (both early and late infections)
 - **CSF examination normal in ~30% of cases of ocular syphilis**

Ears

- Sensorineural hearing loss w/vestibular complaints (sudden or fluctuating hearing loss, tinnitus or vertigo)
 - Congenital (early and late)
 - Acquired (secondary and late stages)
 - **CSF examination is normal in >90% of cases of otic syphilis**

***No need for a CSF examination in patients who only have ocular or otic symptoms/signs

SYPHILIS SEROLOGICAL TESTING

Nontreponemal tests

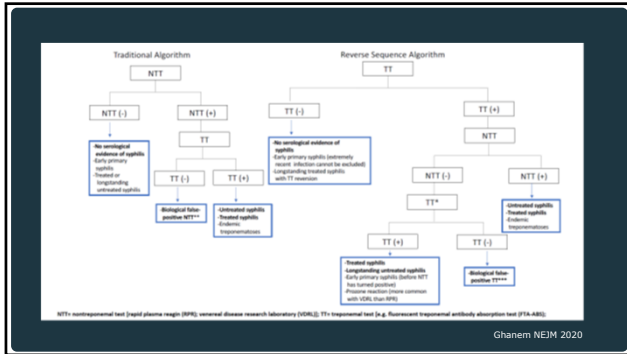
- RPR (serum) or VDRL (serum or CSF)
- False+: endemic treponematoses, old age, pregnancy, autoimmune disease (APS), viral infections
- Reactive result must be confirmed with treponemal test
- False negative: PROZONE effect
- Four-fold (i.e. 2-dilution) decline after treatment = CURE (irrespective of the end-titer)
- **Titers will decline with or without treatment**

Treponemal tests

- MHA-TP, TPPA, FTA-Abs, EIAs, CIA
- Detect IgG +/- IgM antibodies against treponemal antigens
- **Once reactive, always reactive even after appropriate therapy**
- False + may occur with endemic treponemal infections (e.g. yaws, pinta, bejel), with Lyme disease, or rarely in autoimmune conditions

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SYPHILIS: DIAGNOSTICS

- Darkfield microscopy or PCR for **genital ulcers** of primary syphilis; **sensitivity of serology in primary syphilis only ~70%**
- **Sensitivity of serology for secondary or early latent syphilis ~100%**
- Over time, non-treponemal serological titers decline and may become nonreactive even in the absence of therapy while treponemal titers remain reactive for life*



NEUROSYPHILIS: DIAGNOSTICS

- No single test can be used to diagnose neurosyphilis
 - 50% of neurosyphilis cases may have negative CSF VDRL; it is highly specific, but **insensitive**
 - CSF treponemal tests are very sensitive but NOT specific (i.e. high false+)
 - May be used to **rule out** neurosyphilis
 - ~30% of persons with LATE neurosyphilis may have nonreactive SERUM nontreponemal test

SYPHILIS THERAPY

- Early stages (primary, secondary, early latent)
 - 2.4 MU of long-acting benzathine penicillin or doxycycline 100mg PO BID X 14 days
- Late latent/unknown duration
 - 2.4 MU of long acting benzathine penicillin G IM X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg po BID X 4 weeks

SYPHILIS THERAPY CONTINUED

- Neurosyphilis/Ocular/Otic syphilis
 - Aqueous penicillin 18 to 24 MU IV X 10-14 days
 - Procaine penicillin 2.4 MU IM qd + probenecid 500 mg po QID X 10-14 days
 - Ceftriaxone 1-2g IV/IM X 10-14 days (2nd line regimen)
- Jarisch-Herxheimer: within 6 hours (up to 24 hours) after therapy of (usually) early syphilis; antipyretics only; **may induce early labor**

QUESTION #2

A pregnant woman living with HIV (CD4 260 cells/mm³; HIV RNA <50 copies/ml) on ART presents with a diffuse rash.

On examination, she has a temperature of 38.3°C and a macular rash on her trunk and extremities including her palms.

Serum RPR is reactive at a titer of 1:2048 and FTA-ABS is reactive

She has a history of severe hives to penicillin but has tolerated cephalosporins.

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QUESTION #2

Which of the following antibiotics is most appropriate?

- A. Azithromycin
- B. Benzathine penicillin G
- C. Ceftriaxone
- D. Doxycycline

SYPHILIS & HIV

- Clinical manifestations similar but timeline may be compressed
 - PWH more susceptible to early neurosyphilis
- Testing and therapy similar to HIV-uninfected
- Serological failure is more likely among PWH
- Serological response may be slower among PWH
- Follow-up is more frequent (every 3 months)

SYPHILIS & PREGNANCY

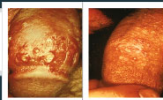
- Screen all women at 1st prenatal visit
- Screen all high risk women and those women living in high-prevalence areas twice in the 3rd trimester: at 28 weeks and again at the time of delivery
- Screen all women who deliver a stillborn infant after 20 weeks' gestation
- **Pregnant penicillin-allergic women with syphilis need to be desensitized to penicillin and treated with a penicillin-based regimen. There are NO OTHER OPTIONS (not even ceftriaxone)**

HSV TAKE-HOME MESSAGES

- Both HSV-1 (particularly among young women and MSM) and 2 cause genital infections
- Most people are unaware that they are infected
- Asymptomatic shedding is the most common reason for transmission
- Condoms and antiviral suppressive therapy decrease risk of male to female transmission by 30% and 55% over time, respectively (condoms less effective from female to male)
- Currently, no formal screening recommendations
- C-section ONLY in women who have active lesions at the time of delivery

HSV

- Both HSV-1 and HSV-2 cause genital disease
- HSV-1 is now a more frequent cause of genital disease (especially in young women and MSM)
- In general, HSV-1 recurrences are less severe and less frequent and asymptomatic shedding is less frequent
- Prior infection with HSV-1 may attenuate severity of HSV-2 infection
- **HSV suppressive therapy in PWH with a history of HSV and who are starting ART- but only if their CD4 <200 cells/mm³**



HSV: DIAGNOSTICS IN PATIENTS WITH GENITAL ULCERS

- Tzanck smear (40% sensitive)
- Culture (sensitivity 30-80%)
 - Mainly used for antiviral susceptibility testing
- Antigen detection (~70% sensitive)
- PCR (FDA cleared, >90% sensitive)
 - **Preferred diagnostic test when a lesion is present**

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HSV: DIAGNOSTICS IN ASYMPTOMATIC PATIENTS

- Use Glycoprotein G-based type-specific EIA assays
 - If gG2 is reactive, patient has genital herpes*
 - If gG1 is reactive, patient either has oral herpes or genital herpes**
- Positive predictive value is low in low prevalence settings
- Serologic testing **NOT** routinely recommended for screening
- Never obtain IgM or try to interpret IgM results!

* Assay has low specificity depending on EIA index value cutoff; for an EIA cutoff <3, a second confirmatory test that uses a different HSV antigen must be performed (HSV Biokit or HSV Western Blot)

** Assay has low sensitivity

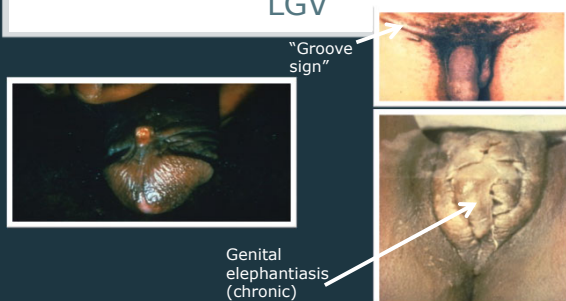
HSV: PREGNANCY

- Risk of vertical transmission if mom acquires FIRST episode (i.e. primary infection) of herpes at time of delivery= up to 80%
- Risk of vertical transmission if mom has RECURRENT episode of herpes at time of delivery <1%
- C-sections are recommended ONLY IF ACTIVE LESIONS OR PRODROMAL SYMPTOMS (i.e. vulvar pain/burning) PRESENT AT DELIVERY
 - ACOG: "For women with a primary or nonprimary first-episode genital HSV infection during the 3rd trimester of pregnancy, cesarean delivery MAY BE OFFERED due to the possibility of prolonged shedding", *ACOG Practice Bulletin #220, May 2020*
- Efficacy data on routine acyclovir use during 3rd trimester of pregnancy to prevent HSV vertical transmission are lacking.
 - ACOG: Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation *ACOG Practice Bulletin #220, May 2020 & Cochrane Systematic Review 2008: <https://doi.org/10.1002/14651858.CD004946.pub2>*

CHLAMYDIA TRACHOMATIS L1-L3: LGV

- Classical manifestation is a short-lived **painless** genital ulcer accompanied by **painful** inguinal lymphadenopathy
- Outbreaks in US and Western Europe associated with **proctitis** particularly among MSM*****
 - Rectal pain, tenesmus, rectal bleeding/discharge
 - May be mistaken for inflammatory bowel disease histologically (early syphilitic proctitis may also be mistaken for IBD on histology)

LGV



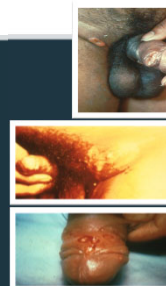
LGV DIAGNOSIS & THERAPY

- **Routine NAATs** do not distinguish between serotypes D-K and L1-L3 (LGV). **Multiplex PCR** can be performed for specific serotypes but is NOT commercially available. Serology is NOT standardized and is NOT recommended
- Therapy: **doxycycline 100mg PO BID X 3* weeks (preferred)** or azithromycin 1g PO q week X 3 weeks (alternate)

*Small observational study suggests that in mild LGV proctitis, 1 week of doxycycline or 2g of azithromycin is sufficient

CHANCROID

- *Haemophilus ducreyi*
 - Endemic in parts of the southern US/ Rates have gone down
 - Increased risk with HIV infection and commercial sex work
- Symptoms: painful, indurated, "ragged" genital ulcers & tender suppurative inguinal adenopathy (50%); kissing lesions on thigh; 10% of patients co-infected with syphilis or HSV; bacterial superinfection not uncommon
- Dx: culture (80% sensitive) [antigen detection and PCR not widely available]
- Rx: Azithromycin 1g PO X1 OR Ceftriaxone 250mg IM X1 (erythromycin and ciprofloxacin may also be used)
- Treat all partners in preceding 60 days



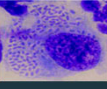


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GRANULOMA INGUINALE OR DONOVANOSIS

- *Klebsiella granulomatis* (*Calymmatobacterium granulomatis*)
- Not endemic in US; common in SE Asia (India), & Southern Africa (recently eradicated in Australia)
- Painless, progressive (destructive), "serpiginous" ulcerative lesions, without regional LAD (pseudobuboes occasionally); beefy red with white border & highly vascular
- Dx: tissue biopsy (no culture test; PCR not FDA cleared); demonstrating the organisms in macrophages, called **Donovan bodies**, using **Wright-Giemsa** stain (NOT Gram's stain)
- Rx: Doxycycline 100mg PO BID X 3 weeks (or until resolution) OR azithromycin 1g PO q week X3 (can also use trimethoprim/sulfa)

GUD	Pain	Characteristics	Diagnosis	Treatment
HSV 1 & 2	Painful	Multiple, superficial, vesicular/ulcerative, erythematous base	-NAATs -Culture (sensitivity ~70%) -Serology	-Acyclovir etc. -Foscarnet (resistant HSV) -Cidofovir parenteral or topical (resistant HSV)
Syphilis (<i>T. pallidum</i>)	Painless	Single, well circumscribed, heaped-up borders, clean base	- Serology - PCR	-Penicillin (preferred) -Doxycycline (alternate for early and late latent)
Chancroid (<i>H. ducreyi</i>)	Painful	Indurated, tender suppurative inguinal LAD (50%); kissing lesions on thigh	- Culture - PCR	-Azithromycin -Ceftriaxone -Erythromycin -Ciprofloxacin
LGV (<i>C. trachomatis</i>)	Painless	short-lived ulcer, painful suppurative LAD, "groove sign" PROCTITIS	- NAATs - Serology - Culture (rarely)	-Doxycycline (preferred) -Azithromycin (alternate)
Granuloma Inguinale (<i>Klebsiella granulomatis</i>)	Painless	Progressive "serpiginous" without LAD; beefy red with white border & highly vascular	- Biopsy	-Doxycycline -Azithromycin -Bactrim